IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Gantier *et al.*	Art Unit	: 1647
Patent No.	: 7,611,700	Examiner	: Stoica, Elly Gerald
Issue Date	: November 3, 2009	Conf. No.	: 7681
Serial No.	: 10/658,834	Cust. No.	: 77202
Filed	: September 8, 2003		
Title	: PROTEASE RESISTANT MODIFIED INTERFERON ALPHA POLYPEPTIDES		

Attn.: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION

Dear Sir:

Pursuant to 37 C.F.R. § 1.322, the patentee respectfully requests that a Certificate of Correction be issued for the above referenced patent to correct the following errors:

IN THE SPECIFICATION

At column 7, lines 15-16, please replace "SEQ ID Nos: 233-289), 989-1015, and 1016-1302)compared" with — SEQ ID Nos: 233-289, 989-1015, and 1016-1302) compared —;

At column 7, line 47, please replace "(SEQ ID NO:216)based" with —(SEQ ID NO:216) based —;

At column 7, lines 51-52, please replace "SEQ ID Nos: 794-849), compared" with — SEQ ID Nos: 794-849) compared —;

At column 7, lines 57-58, please replace "SEQ ID Nos: 896-939), compared" with — SEQ ID Nos: 896-939) compared —;

At column 7, line 64, please replace "(SEQ ID NO:211),based" with —(SEQ ID NO:211), based —;

At column 8, line 2, please replace "SEQ ID Nos: 729-760), compared" with — SEQ ID Nos: 729-760) compared —;

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
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Date of Deposit: March 22, 2010
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Certificate of Correction Branch Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Jon Levy

At column 8, lines 8-9, please replace "SEQ ID Nos: 761-763), compared" with — SEQ ID Nos: 761-763) compared —;

At column 8, lines 16-17, please replace "Nos: 940-977), compared to the wild-type sequence (SEQ ID NO: 201),based" with — Nos: 940-977) compared to the wild-type sequence (SEQ ID NO: 201), based —;

At column 8, lines 21-22, please replace "SEQ ID Nos: 401-428), compared to residues 1-1000" with —SEQ ID Nos: 401-428) compared to residues 1-100—;

At column 8, lines 29-30, please replace "SEQ ID Nos: 362-400), compared to the wild-type sequence (SEQ ID NO: 202),based" with — SEQ ID Nos: 362-400) compared to the wild-type sequence (SEQ ID NO: 202), based —;

At column 8, lines 35-36, please replace "SEQ ID Nos: 603-630), compared" with — SEQ ID Nos: 603-630) compared —;

At column 8, lines 40-41, please replace "SEQ ID Nos: 429-476), compared" with — SEQ ID Nos: 429-476) compared —;

At column 8, lines 46-47, please replace "SEQ ID Nos:477-498), compared" with — SEQ ID Nos: 477-498) compared —;

At column 8, lines 52-53, please replace "SEQ ID Nos: 543-567), compared" with — SEQ ID Nos: 543-567) compared —;

At column 8, lines 58-59, please replace "SEQ ID Nos: 568-602), compared" with — SEQ ID Nos: 568-602) compared —;

At column 8, lines 64-65, please replace "SEQ ID Nos: 499-542), compared" with — SEQ ID Nos: 499-542) compared —;

At column 47, line 50, please replace "IFNαcytokines" with —IFNα cytokines —;

At column 47, line 57, please replace "herein The" with —herein. The—;

At column 52, line 41, please replace "10/658,355,filed" with —10/658,355, filed —;

At column 66, line 50, please replace "prostatate" with —prostate—;

At column 74, line 29, please replace "alicuots" with —aliquots—;

At column 74, line 33, please replace "analysis.Residual" with —analysis. Residual—;

At column 74, line 26, please replace "IFN α" with — IFN-α —.

IN THE CLAIMS

Please replace Claim 1 and Claim 2 with the following amended claims:

1. An isolated interferon (IFN) alpha cytokine, comprising an amino acid replacement in its sequence of amino acids, wherein:

an amino acid replacement is ~~E41 Q~~ E41Q, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis so that it can be administered orally compared to the unmodified interferon alpha cytokine that does not comprise the amino acid replacement; and

in the interferon-alpha cytokine[[,]]

the interferon is not glycosylated at E41Q; and

the unmodified interferon alpha cytokine is selected from among an interferon α-2b (IFNα-2b), an interferon α-2a (IFNα-2a), an interferon α-2c (IFNα-2c) and consensus interferon whose sequences are set forth in SEQ ID Nos. 1, 182, 185 and 232, respectively.

2. An interferon alpha cytokine selected from among IFNα-2b, IFNα-2a, IFNα-2c, consensus interferon, IFNα-c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F and IFNα-8, each comprising the modification E41Q, wherein:

the sequence of a human wild-type interferon alpha for each of IFNα-2b, IFNα-2a, IFNα-2c, consensus interferon, IFNα-c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F and IFNα-8; is set forth in SEQ ID Nos. 1, 182, 185, 232, 183 and 186-195, respectively; the modification at E41Q increases resistance of the interferon alpha cytokine so that it can be administered orally[[.]];

the interferon alpha cytokine is not glycosylated at E41Q; and

residue 1 in each SEQ ID corresponds to residue 1 of the mature interferon-alpha.

REMARKS

A Certificate of Correction (Form PTO-1050) incorporating the above changes is included with this Request. Since all the errors are those of the Patent Office, no fee should be due. However, if it is determined a fee is due, the Office is hereby authorized to charge the fee to Deposit Account No. 02-1818.

IN THE SPECIFICATION:

This Certificate of Correction seeks to correct errors introduced by the PTO. For example, the corrections at columns 7 and 8 seek to incorporate amendments made to the Specification, found on pages 2-6 of the Preliminary Amendment, mailed on July 11, 2005. A copy of the date stamped Preliminary Amendment is attached herewith as evidence. The corrections at columns 42, 52, 66 and 74 seek to incorporate amendments made to the Specification, found on pages 9-10, 14 and 17 of the Preliminary Amendment, mailed on April 8, 2004. A copy of the date stamped Preliminary Amendment is attached herewith as evidence.

IN THE CLAIMS:

This Certificate of Correction also seeks to correct obvious typographical errors in the Claims which were introduced by the PTO. Claim 1 is amended to correct the typographical errors in which a space was inserted in "E41 Q" such that the phrase now reads "E41Q", and a comma was inserted after the word "cytokine," such that the phrase now reads "in the interferon-alpha cytokine the interferon is not glycosylated". Claim 2 are amended to correct the typographical error in which a "." was recited instead of a ";" in the middle of the claim.

Accordingly, none of the requested changes constitute new matter. Patentee respectfully requests correction of errors by issuance of a Certificate of Correction.

Respectfully submitted,

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Reg. No. 33,779

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. .: 7,611,700

APPLICATION NO .: 10/658,834

DATED .: NOVEMBER 3, 2009

INVENTOR(S) .: GANTIER ET AL.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE SPECIFICATION:

At column 7, lines 15-16, please replace "SEQ ID Nos: 233-289), 989-1015, and 1016-1302)compared" with — SEQ ID Nos: 233-289, 989-1015, and 1016-1302) compared —;

At column 7, line 47, please replace "(SEQ ID NO:216)based" with —(SEQ ID NO:216) based —;

At column 7, lines 51-52, please replace "SEQ ID Nos: 794-849), compared" with — SEQ ID Nos: 794-849) compared —;

At column 7, lines 57-58, please replace "SEQ ID Nos: 896-939), compared" with — SEQ ID Nos: 896-939) compared —;

At column 7, line 64, please replace "(SEQ ID NO:211),based" with —(SEQ ID NO:211), based —;

At column 8, line 2, please replace "SEQ ID Nos: 729-760), compared" with — SEQ ID Nos: 729-760) compared —;

At column 8, lines 8-9, please replace "SEQ ID Nos: 761-763), compared" with — SEQ ID Nos: 761-763) compared —;

At column 8, lines 16-17, please replace "Nos: 940-977), compared to the wild-type sequence (SEQ ID NO: 201),based" with — Nos: 940-977) compared to the wild-type sequence (SEQ ID NO: 201), based —;

At column 8, lines 21-22, please replace "SEQ ID Nos: 401-428), compared to residues 1-1000" with —SEQ ID Nos: 401-428) compared to residues 1-100—;

At column 8, lines 29-30, please replace "SEQ ID Nos: 362-400), compared to the wild-type sequence (SEQ ID NO: 202),based" with — SEQ ID Nos: 362-400) compared to the

MAILING ADDRESS OF SENDER:

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wild-type sequence (SEQ ID NO: 202), based —;

At column 8, lines 35-36, please replace "SEQ ID Nos: 603-630), compared" with — SEQ ID Nos: 603-630) compared —;

At column 8, lines 40-41, please replace "SEQ ID Nos: 429-476), compared" with — SEQ ID Nos: 429-476) compared —;

At column 8, lines 46-47, please replace "SEQ ID Nos:477-498), compared" with — SEQ ID Nos: 477-498) compared —;

At column 8, lines 52-53, please replace "SEQ ID Nos: 543-567), compared" with — SEQ ID Nos: 543-567) compared —;

At column 8, lines 58-59, please replace "SEQ ID Nos: 568-602), compared" with — SEQ ID Nos: 568-602) compared —;

At column 8, lines 64-65, please replace "SEQ ID Nos: 499-542), compared" with — SEQ ID Nos: 499-542) compared —;

At column 47, line 50, please replace "IFNαcytokines" with —IFNα cytokines —;

At column 47, line 57, please replace "herein The" with —herein. The—;

At column 52, line 41, please replace "10/658,355,filed" with —10/658,355, filed —;

At column 66, line 50, please replace "prostatate" with —prostate—;

At column 74, line 29, please replace "alicuots" with —aliquots—;

At column 74, line 33, please replace "analysis.Residual" with —analysis. Residual—;

At column 74, line 26, please replace "IFN α" with — IFN-α —.

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PATENT NO. .: 7,611,700

APPLICATION NO .: 10/658,834

DATED .: NOVEMBER 3, 2009

INVENTOR(S) .: GANTIER ET AL.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

Column 87, line 32 to Column 87, line 47

1. An isolated interferon (IFN) alpha cytokine, comprising an amino acid replacement in its sequence of amino acids, wherein:

an amino acid replacement is E41Q, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis so that it can be administered orally compared to the unmodified interferon alpha cytokine that does not comprise the amino acid replacement; and

in the interferon-alpha cytokine the interferon is not glycosylated at E41Q; and

the unmodified interferon alpha cytokine is selected from among an interferon α-2b (IFNα-2b), an interferon α-2a (IFNα-2a), an interferon α-2c (IFNα-2c) and consensus interferon whose sequences are set forth in SEQ ID Nos. 1, 182, 185 and 232, respectively.

Column 87, line 48 to Column 87, line 64

2. An interferon alpha cytokine selected from among IFNα-2b, IFNα-2a, IFNα-2c, consensus interferon, IFNα-c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F and IFNα-8, each comprising the modification E41Q, wherein:

the sequence of a human wild-type interferon alpha for each of IFNα-2b, IFNα-2a, IFNα-2c, consensus interferon, IFNα-c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F and IFNα-8; is set forth in SEQ ID Nos. 1, 182, 185, 232, 183 and 186-195, respectively; the modification at E41Q increases resistance of the interferon alpha cytokine so that it can be administered orally;

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PATENT NO. .: 7,611,700

APPLICATION NO .: 10/658,834

DATED .: NOVEMBER 3, 2009

INVENTOR(S) .: GANTIER ET AL.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

the interferon alpha cytokine is not glycosylated at E41Q; and
residue 1 in each SEQ ID corresponds to residue 1 of the mature interferon-alpha.

MAILING ADDRESS OF SENDER:

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PRELIMINARY AMENDMENT
DATED JULY 11, 2005

Attorney's Docket No.: 17109-012001/922

7-13-05

IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Rene Gantier et al.	Art Unit	: 1646
Serial No.	: 10/658,834	Examiner	: Prema Maria Mertz
Filed	: September 8, 2003	Cust. No.	: 20985
Conf. No.	: 7681		
Title	: RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY, THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

THIRD PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to the examination of the above-captioned application, please amend the application as follows.

Amendments to the specification begin on page 2 of this paper.

Amendments to the claims begin on page 8 of this paper.

Amendments to the Figures begin on page 69 of this paper.

Amendments to the Sequence Listing begin on page 70 of this paper.

Remarks/Arguments begin on page 71 of this paper.

An Appendix begins on page 82 of this paper and includes annotated paper copies of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, 1043, a substitute Sequence Listing, a computer-readable form of the Sequence Listing, a Verified Statement that the computer-readable form is identical to the substitute Sequence Listing, and a Replacement Sheet of Fig. 9.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number EV 399296908 US
Date of Deposit July 11, 2005
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Stephanie Seidman

AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 11, line 11 with the following amended paragraph:

Figure 9 illustrates a structural alignment of a number of cytokines and interferon α-2b sequences (SEQ ID NO: 1 (IFN-α2b)); SEQ ID NO: 196 (IFN-β); SEQ ID NO: 201 (EPO); and SEQ ID NO: 210 (G-CSF)). Bold underlined residues define the region on each cytokine sequence that based on structural homology comparison corresponds to the structurally-related mutations found on the LEADs for protease resistance of IFNα-2b.

Please replace the paragraph beginning at page 11, line 29 with the following amended paragraph:

Figure 12 (A) shows a representative number of the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interferon β (corresponding to SEQ ID Nos: 233-289, 989-1015, and 1016-1302) compared to the wild-type sequence (SEQ ID NO: 196), based on 3D-scanning (structural homology method), including PAM250 analysis.

Please replace the paragraph beginning at page 12, line 3 with the following amended paragraph:

Figure 12 (B) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interferon gamma (corresponding to SEQ ID Nos: 290-311) compared to residues 1-100 of the wild-type sequence (SEQ ID NO: 199), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 7 with the following amended paragraph:

Figure 12 (C) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-10 (corresponding to SEQ ID Nos: 312-361) compared to residues 1-100 of the wild-type sequence (SEQ ID NO: 200), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 11 with the following amended paragraph:

Figure 12 (D) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of ciliary neurotrophic factor (corresponding

to SEQ ID Nos: 684-728) compared to residues 51-188 of the wild-type sequence (SEQ ID NO: 212), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 15 with the following amended paragraph:

Figure 12 (E) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of granulocyte-colony stimulating factor (corresponding to SEQ ID Nos: 631-662) compared to residues 51-177 of the wild-type sequence (SEQ ID NO: 210), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 19 with the following amended paragraph:

Figure 12 (F) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of human growth hormone (corresponding to SEQ ID Nos: 850-895) compared to residues 51-191 of the wild-type sequence (SEQ ID NO: 216), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 23 with the following amended paragraph:

Figure 12 (G) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-12 (corresponding to SEQ ID Nos: 794-849) compared to residues 51-197 of the wild-type sequence (SEQ ID NO: 215), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 27 with the following amended paragraph:

Figure 12 (H) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-6 (corresponding to SEQ ID Nos: 896-939) compared to residues 51-183 of the wild-type sequence (SEQ ID NO: 217), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 1 with the following amended paragraph:

Figure 12 (I) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of leptin (corresponding to SEQ ID Nos:

663-683) compared to the wild-type sequence (SEQ ID NO: 211), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 5 with the following amended paragraph:

Figure 12 (J) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of leukemia inhibitory factor (corresponding to SEQ ID Nos: 729-760) compared to residues 51-180 of the wild-type sequence (SEQ ID NO: 213), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 9 with the following amended paragraph:

Figure 12 (K) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of oncostatin M (corresponding to SEQ ID Nos: 761-793) compared to residues 51-150 of the wild-type sequence (SEQ ID NO: 214), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 13 with the following amended paragraph:

Figure 12 (L) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of erythropoietin (corresponding to SEQ ID Nos: 940-977) compared to the wild-type sequence (SEQ ID NO: 201), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 17 with the following amended paragraph:

Figure 12 (M) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of Flt3 ligand (corresponding to SEQ ID Nos: 401-428) compared to residues 1-100 of the wild-type sequence (SEQ ID NO: 203), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 21 with the following amended paragraph:

Figure 12 (N) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of granulocyte-macrophage colony-

stimulating factor (corresponding to SEQ ID Nos: 362-400) compared to the wild-type sequence (SEQ ID NO: 202), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 25 with the following amended paragraph:

Figure 12 (O) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-13 (corresponding to SEQ ID Nos: 603-630) compared to the wild-type sequence (SEQ ID NO: 209), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 29 with the following amended paragraph:

Figure 12 (P) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-2 (corresponding to SEQ ID Nos: 429-476) compared to the wild-type sequence (SEQ ID NO: 204), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 3 with the following amended paragraph:

Figure 12 (Q) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-3 (corresponding to SEQ ID Nos: 477-498) compared to the wild-type sequence (SEQ ID NO: 205), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 7 with the following amended paragraph:

Figure 12 (R) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-4 (corresponding to SEQ ID Nos: 543-567) compared to the wild-type sequence (SEQ ID NO: 207), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 11 with the following amended paragraph:

Figure 12 (S) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-5 (corresponding to SEQ ID

Nos: 568-602) compared to the wild-type sequence (SEQ ID NO: 208), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 15 with the following amended paragraph:

Figure 12 (T) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of stem cell factor (corresponding to SEQ ID Nos: 499-542) compared to residues 1-141 of the wild-type sequence (SEQ ID NO: 206), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 61, line 3 with the following amended paragraph:

As set forth in Example 2, the 3-dimensional structure of IFNα-2b obtained from the NMR structure of IFNα-2a (PDB code 1ITF) was used to select only those residues exposed to solvent from a list of residues along the IFNα-2b and IFNα-2a sequence which can be recognized as a substrate for different enzymes present in the serum. Residue 1 corresponds to the first residue of the mature peptide IFNα-2b (SEQ ID NO:1) encoded by nucleotides 580-1074 of sequence accession No. J00207~~, SEQ ID NO:1~~. Using this approach, the following 42 amino acid target positions were identified as is-HITs on IFNα-2b or IFNα-2a, which numbering is that of the mature protein (SEQ ID NO:1 or SEQ ID NO:182, respectively): L3, P4, R12, R13, M16, R22, K23 or R23, F27, L30, K31, R33, E41, K49, E58, K70, E78, K83, Y89, E96, E107, P109, L110, M111, E113, L117, R120, K121, R125, L128, K131, E132, K133, K134, Y135, P137, M148, R149, E159, L161, R162, K164, and E165. Each of these positions was replaced by residues defined as compatible by the substitution matrix PAM250 while at the same time not generating any new substrates for proteases. For these 42 is-HITs, the residue substitutions determined by PAM250 analysis were as follows:

Please replace the paragraph beginning at page 64, line 16 with the following amended paragraph:

Also provided herein are modified IFNα-2b or IFNα-2a cytokines selected from among proteins comprising one or more single amino acid replacements in SEQ ID NOS:1 or 182, corresponding to the replacement of: N by D at position 45 ~~(e.g., SEQ ID NO:978)~~; D by G at position 94 ~~(e.g, SEQ ID NO:979)~~; G by R at position 102 ~~(e.g., SEQ ID NO:980)~~; A

by G at position 139 ~~(e.g., SEQ ID NO:981)~~; or any combination thereof. These particular proteins have also been found herein to have increased resistance to proteolysis.

Please delete the following paragraph beginning at page 89, line 26 to page 89, line 31:

A modified IFNβ-1 cytokine, comprising mutations ... of the native amino acid residue(s).

Please delete the following paragraph beginning at page 90, line 1 to page 90, line 6:

A modified IFNβ-2a cytokine, comprising mutations ... of the native amino acid residue(s).

Please replace the 7th row of Table 3 on page 142 of the specification with the following amended row:

c37-39	[[147]]	G37N/P39S	147	G37N/P39T

Please replace the paragraph beginning at page 148, line 14 of the specification with the following amended paragraph:

Four mutants with mutations ~~to additional~~ in addition to those selected by ~~the~~ rational mutagenesis were generated in the *E. coli* MutS strain and were detected by sequencing. The mutants were the following: E41Q/ D94G ~~SEQ.ID No. 199~~; L117V/ A139G ~~SEQ.ID No. 204~~; E41H/ Y89H/ N45D ~~SEQ.ID No. 198~~; and K121Q/ P109A/ K133Q/ G102R ~~SEQ.ID No. 204~~.

AMENDMENTS TO THE CLAIMS:

This listing of claims replaces all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Previously presented) A modified cytokine that exhibits increased resistance to proteolysis compared to the unmodified cytokine or a modified cytokine selected from the group consisting of modified cytokines comprising a sequence of amino acids set forth in any of SEQ ID NOS: 2-181, 233-1303 or a structural homolog thereof.

2. (Currently amended) The modified cytokine of claim 1, selected from ~~the group consisting of~~ a member of the interferons/interleukin-10 protein family, a member of the long-chain cytokine family and a member of the short-chain cytokine family, wherein the modified cytokine is a modified interferon α of any of SEQ ID NOS: 87, 89, 90, 93, 96, 101, 103, 107, 124, 979, 980, 983, 984, 985, 986 and 987 or a cytokine modified on the basis of 3-dimensional structural homology with any of SEQ ID NOS: 87, 89, 90, 93, 96, 101, 103, 107, 124, 979, 980, 983, 984, 985, 986 and 987.

3. (Currently amended) The modified cytokine of claim 1 selected from ~~the group consisting of~~ interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha-2a (IFNα-2a), interferon alpha-2b (IFNα-2b), and interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

4. (Original) The modified cytokine of claim 1, that is an interferon.

5. (Previously presented) The modified cytokine of claim 1, that is an interferon α-2b (IFNα-2b), interferon α-2a (IFNα-2a), interferon α-2c (IFNα-2c) or an interferon having the sequence set forth in SEQ ID NO: 232.

6. (Currently amended) A modified cytokine of claim 4, that is IFNα-2b or IFNα-2a or IFNα-2C selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements in SEQ ID NOS: 1 or 182, corresponding to the replacement of: L by V at position 3; L by I at position 3; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by

V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165,

wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

7. (Currently amended) The modified cytokine of claim 6, wherein:

the protein is human;

has more resistance to proteolysis than the unmodified protein; and

the protein is selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements in SEQ ID NOS:1 or 182, corresponding to: F by V at position 27; R by H at position 33; E by Q at position 41; E by H at position 41; E by Q at position 58; E by H at position 58; E by Q at position 78; E by H at position 78; Y by H at position 89; E by Q at position 107; E by H at position 107; P by A at position 109; L by V at position 110; M by V at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; K by Q at position 133; K by T at position 133; E by Q at position 159 and E by H at position 159.

8. (Currently amended) A modified IFNα-2b or IFNα-2a cytokine of claim 5 selected from ~~the group consisting of~~ proteins comprising one or more sets of dual-amino acid replacements in SEQ ID NOS:1 or 182, corresponding to:

D by N at position 2 and P by S at position 4;

D by N at position 2 and P by T at position 4;
L by N at position 3 and Q by S at position 5;
L by N at position 3 and Q by T at position 5;
P by N at position 4 and T by S at position 6;
P by N at position 4 and T by T at position 6;
Q by N at position 5 and H by S at position 7;
Q by N at position 5 and H by T at position 7;
T by N at position 6 and S by S at position 8;
T by N at position 6 and S by T at position 8;
H by N at position 7 and L by S at position 9;
H by N at position 7 and L by T at position 9;
S by N at position 8 and G by S at position 10;
S by N at position 8 and G by T at position 10;
L by N at position 9 and S by S at position 11;
L by N at position 9 and S by T at position 11;
M by N at position 21 and K by S at position 23;
M by N at position 21 and K by T at position 23;
R by N at position 22 and I by S at position 24;
R by N at position 22 and I by T at position 24;
R or K by N at position 23 and S by S at position 25;
R or K by N at position 23 and S by T at position 25;
I by N at position 24 and L by S at position 26;
I by N at position 24 and L by T at position 26;
S by N at position 25 and F by S at position 27;
S by N at position 25 and F by T at position 27;
L by N at position 26 and S by S at position 28;
L by N at position 26 and S by T at position 28;
S by N at position 28 and L by S at position 30;
S by N at position 28 and L by T at position 30;
L by N at position 30 and D by S at position 32;
L by N at position 30 and D by T at position 32;
K by N at position 31 and R by S at position 33;
K by N at position 31 and R by T at position 33;
D by N at position 32 and H by S at position 34;
D by N at position 32 and H by T at position 34;
R by N at position 33 and D by S at position 35;

R by N at position 33 and D by T at position 35;
H by N at position 34 and F by S at position 36;
H by N at position 34 and F by T at position 36;
D by N at position 35 and G by S at position 37;
D by N at position 35 and G by T at position 37;
F by N at position 36 and F by S at position 38;
F by N at position 36 and F by T at position 38;
G by N at position 37 and P by S at position 39;
G by N at position 37 and P by T at position 39;
F by N at position 38 and Q by S at position 40;
F by N at position 38 and Q by T at position 40;
P by N at position 39 and E by S at position 41;
P by N at position 39 and E by T at position 41;
Q by N at position 40 and E by S at position 42;
Q by N at position 40 and E by T at position 42;
E by N at position 41 and F by S at position 43;
E by N at position 41 and F by T at position 43;
E by N at position 42 and G by S at position 44;
E by N at position 42 and G by T at position 44;
F by N at position 43 and N by S at position 45;
F by N at position 43 and N by T at position 45;
G by N at position 44 and Q by S at position 46;
G by N at position 44 and Q by T at position 46;
N by N at position 45 and F by S at position 47;
N by N at position 45 and F by T at position 47;
Q by N at position 46 and Q by S at position 48;
Q by N at position 46 and Q by T at position 48;
F by N at position 47 and K by S at position 49;
F by N at position 47 and K by T at position 49;
Q by N at position 48 and A by S at position 50;
Q by N at position 48 and A by T at position 50;
K by N at position 49 and E by S at position 51;
K by N at position 49 and E by T at position 51;
A by N at position 50 and T by S at position 52;
A by N at position 50 and T by T at position 52;
S by N at position 68 and K by S at position 70;

S by N at position 68 and K by T at position 70;
K by N at position 70 and S by S at position 72;
K by N at position 70 and S by T at position 72;
A by N at position 75 and D by S at position 77;
A by N at position 75 and D by T at position 77;
D by N at position 77 and T by S at position 79;
D by N at position 77 and T by T at position 79;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
Q by N at position 101 and V by S at position 103;
Q by N at position 101 and V by T at position 103;
G by N at position 102 and G by S at position 104;
G by N at position 102 and G by T at position 104;
V by N at position 103 and V by S at position 105;
V by N at position 103 and V by T at position 105;
G by N at position 104 and T by S at position 106;
G by N at position 104 and T by T at position 106;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;
E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;
T by N at position 108 and I by S at position 110;
T by N at position 108 and I by T at position 110;
K by N at position 134 and S by S at position 136;
K by N at position 134 and S by T at position 136;
S by N at position 154 and N by S at position 156;
S by N at position 154 and N by T at position 156;
T by N at position 155 and L by S at position 157;
T by N at position 155 and L by T at position 157;
N by N at position 156 and Q by S at position 158;
N by N at position 156 and Q by T at position 158;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
Q by N at position 158 and S by S at position 160;

Q by N at position 158 and S by T at position 160;
E by N at position 159 and L by S at position 161;
E by N at position 159 and L by T at position 161;
S by N at position 160 and R by S at position 162;
S by N at position 160 and R by T at position 162;
L by N at position 161 and S by S at position 163;
L by N at position 161 and S by T at position 163;
R by N at position 162 and K by S at position 164;
R by N at position 162 and K by T at position 164;
S by N at position 163 and E by S at position 165; and
S by N at position 163 and E by T at position 165,
wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

9. (Currently amended) A modified IFNα-2b or IFNα-2a mutant cytokine of claim 5 selected from ~~the group consisting of~~ proteins comprising one or more sets of dual amino acid replacements in SEQ ID NOS:1 or 182, corresponding to:
Q by N at position 5 and H by S at position 7;
P by N at position 39 and E by S at position 41;
P by N at position 39 and E by T at position 41;
Q by N at position 40 and E by S at position 42;
Q by N at position 40 and E by T at position 42;
E by N at position 41 and F by S at position 43;
E by N at position 41 and F by T at position 43;
F by N at position 43 and N by S at position 45;
G by N at position 44 and Q by T at position 46;
N by N at position 45 and F by S at position 47;
N by N at position 45 and F by T at position 47;
Q by N at position 46 and Q by S at position 48;
F by N at position 47 and K by S at position 49;
F by N at position 47 and K by T at position 49;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;

E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
E by N at position 159 and L by S at position 161; and
E by N at position 159 and L by T at position 161.

10. (Original) A modified cytokine of claim 5, further comprising one or more pseudo-wild type mutations.

11. (Original) The modified cytokine of claim 10 that is IFNα-2b or IFNα-2a.

12. (Currently amended) A modified IFNα-2b or IFNα-2a cytokine of claim 11, comprising one or more pseudo-wild type mutations at amino acid positions of IFNα-2b or IFNα-2a corresponding to SEQ ID NOS:1 or 182, amino acid residues: 9, 10, 17, 20, 24, 25, 35, 37, 41, 52, 54, 56, 57, 58, 60, 63, 64, 65, 76, 89, and 90, wherein the mutations are selected from ~~the group consisting of~~ one or more of insertions, deletions and replacements of the native amino acid residue(s), wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a protein set forth in SEQ ID NOS:1 or 182.

13. (Previously presented) A modified IFNα-2b or IFNα-2a cytokine of claim 11, comprising one wherein the pseudo-wild type replacements are one or more mutations in SEQ ID NOS: 1 or 182 corresponding to:

P by A at position 4; Q by A at position 5,
T by A at position 6; L by A at position 9,
LG by A at position 10; L by A at position 17,
Q by A at position 20; I by A at position 24,
S by A at position 25; D by A at position 35,
G by A at position 37; G by A at position 39;
E by A at position 41; E by A at position 42
E by A at position 51; T by A at position 52,
P by A at position 54; V by A at position 55
L by A at position 56; H by A at position 57,
E by A at position 58; I by A at position 60,
I by A at position 63; F by A at position 64,
N by A at position 65; W by A at position 76,
D by A at position 77; E by A at position 78
L by A at position 81; Y by A at position 85
Y by A at position 89; Q by A at position 90
G by A at position 104; L by A at position 110

S by A at position 115 and E by A at position 146.

14. (Currently amended) A modified cytokine of claim 5, comprising one or more pseudo-wild type mutations at amino acid positions of IFNα-2b, IFNα-2c or a protein having the sequence set forth in SEQ ID NO: 232 corresponding amino acid residues: 4, 5, 6, 9, 10, 17, 20, 24, 25, 35, 37, 39, 41, 42, 51, 52, 54, 56, 57, 58, 60, 63, 64, 65, 76, 77, 78, 81, 85, 89, 90, 104, 110, 115 and 146 to SEQ ID No. 1, 182 or 232, wherein the mutations are selected from ~~the group consisting of~~ one or more of insertions, deletions and replacements of the native amino acid residue(s), wherein residue 1 corresponds to residue 1 of the mature interferon set forth in SEQ ID NOS: 1, 182 or 232.

15. (Currently amended) The modified cytokine of claim 14, wherein the pseudo-wild type replacements are one or more mutations selected from:

P by A at position 4; Q by A at position 5;
T by A at position 6; L by A at position 9;
LG by A at position 10; L by A at position 17;
Q by A at position 20; I by A at position 24;
S by A at position 25; D by A at position 35;
G by A at position 37; G by A at position 39;
E by A at position 41; E by A at position 42;
E by A at position 51; T by A at position 52;
P by A at position 54; V by A at position 55;
L by A at position 56; H by A at position 57;
E by A at position 58; I by A at position 60;
I by A at position 63; F by A at position 64;
N by A at position 65; W by A at position 76;
D by A at position 77; E by A at position 78;
L by A at position 81; Y by A at position 85;
Y by A at position 89, Q by A at position 90;
G by A at position 104; L by A at position 110;
S by A at position 115 and E by A at position 146, wherein the positions correspond to SEQ ID NOS: 1, 182, 185 or 232.

16. (Original) A modified cytokine of claim 5 that has increased antiviral activity compared to the unmodified cytokine.

17. (Original) The modified cytokine of claim 16, wherein antiviral activity is assessed by measuring replication by reverse transcription quantification PCR (RT-qPCR).

18. (Currently amended) A modified cytokine of claim 5 that has more antiviral activity than anti-proliferative activity compared to the unmodified cytokine.

19. (Currently amended) The modified cytokine of claim 18, wherein anti-proliferative activity is assessed by measuring cell proliferation in the presence of the cytokine.

20. (Currently amended) A modified cytokine of claim 5 that binds to an IFN receptor, but exhibits decreased antiviral activity and decreased anti-proliferative activity relative to its receptor binding activity when compared to the unmodified cytokine.

21. (Original) A modified cytokine of claim 1, comprising two or more mutations.

22. (Original) The modified cytokine of claim 21 that is a modified IFNα-2b cytokine.

23. (Previously presented) A modified cytokine of claim 1, wherein the cytokine comprises the sequence of amino acids set forth in any of SEQ ID NOS: 2 through 181, wherein the arginine at position 23 is replaced with a lysine.

24. (Currently amended) A modified cytokine of any claim 1 selected from ~~the group consisting of~~ interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha (IFNα), interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

25. (Original) A collection of the modified cytokines of claim 1, wherein the modified cytokines contain one or a plurality of mutations.

26. (Original) A nucleic acid molecule encoding a modified cytokine of claim 1.

27. (Original) A vector comprising a nucleic acid molecule of claim 26.

28. (Original) A eukaryotic cell, comprising the vector of claim 27.

29. (Original) A collection of nucleic acid molecules comprising a plurality of the molecules of claim 26.

30. (Original) A collection of nucleic acid molecules comprising a plurality of the vectors of claim 27.

31. (Previously presented) A method for expression of a modified cytokine, comprising:

introducing a nucleic acid of claim 26 into a host; and

culturing the host, under conditions and in which the modified encoded cytokines are expressed.

32. (Original) The method of claim 31, wherein the nucleic acid is introduced into a host cell.

33. (Currently amended) The method of claim 31, wherein the cytokine is a modified IFNα-2b, an IFNα-2a cytokine, an IFNα-2c, or an interferon of SEQ ID NO: 232.

34. (Original) The method of claim 31, wherein the host is a eukaryotic host cell.

35. (Previously presented) The method of claim 31, wherein the cytokine is glycosylated.

36. (Original) The method of claim 31, wherein expression is effected *in vivo*.

37. (Original) The method of claim 31, wherein expression is effected *in vitro*.

38. (Original) The method of claim 31, wherein expression is effected in a cell-free system.

39. (Previously presented) A modified cytokine of claim 2, comprising two or more mutations.

40. (Original) A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

41. (Currently amended) A modified cytokine of claim 5 that exhibits greater resistance to proteolysis compared to the unmodified cytokine, comprising one or more amino acid replacements at one or more positions on the cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNα-2, ~~or~~ IFNα-2a, ~~or~~ IFNα-2c or consensus IFNα of SEQ ID NO: 232.

42. (Currently amended) A modified cytokine of claim 41, wherein the resistance to proteolysis is measured by ~~mixing it~~ mixture with a protease *in vitro*, incubation with blood or incubation with serum.

43. (Currently amended) A modified cytokine of claim 1 that is a structural homolog of IFNα-2b, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of the modified IFNα-2b, ~~or~~ IFNα-2a, ~~or~~ IFNα-2c or an interferon of SEQ ID NO: 232.

44. (Original) A modified cytokine of claim 43, wherein the homolog has increased resistance to proteolysis compared to its unmodified cytokine counterpart, wherein the resistance to proteolysis is measured by mixture with a protease *in vitro*, incubation with blood or incubation with serum.

45. (Original) The cytokine of claim 44 that is an IFNα cytokine.

46. (Currently amended) The cytokine of claim 45, selected from ~~the group consisting of~~ IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, and IFNα-consensus cytokine.

47. (Previously presented) A modified cytokine of claim 1 that is modified IFNα-2a cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 182 in the IFNα-2a corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of unmodified IFNα-2b, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-2a.

48. (Currently amended) The modified IFNα-2a of claim 47, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 182, corresponding to amino acid positions 41, 58, 78, 107, 117, 125, 133 and 159.

49. (Previously presented) A modified IFNα-c cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 183 in the IFNα-c corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-c.

50. (Currently amended) The modified IFNα-c of claim 49, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 183, corresponding to amino acid positions 41, 59, 79, 108, 118, 126, 134 and 160.

51. (Previously presented) A modified IFNα-c, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 185 in the IFNα-2c corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-2c.

52. (Currently amended) The modified IFNα-2c cytokine of claim 51, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 185, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

53. (Previously presented) A modified IFNα-d cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 186 in the

IFNα-d corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-d.

54. (Currently amended) The IFNα-d modified cytokine of claim 53, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 186, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

55. (Previously presented) A modified IFNα-5 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 187 in the IFNα-5 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-5.

56. (Currently amended) The IFNα-5 modified cytokine of claim 55, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 187, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

57. (Previously presented) A modified IFNα-6 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 188 in the IFNα-6 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-6.

58. (Currently amended) The IFNα-6 modified cytokine of claim 57, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 188, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

59. (Previously presented) A modified IFNα-4 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 189 in the IFNα-4 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-4.

60. (Currently amended) The IFNα-4 modified cytokine of claim 59, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single

amino acid replacements in SEQ ID NO: 189, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

61. (Previously presented) A modified IFNα-4b cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 190 in the IFNα-4b corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-4b.

62. (Currently amended) The IFNα-4b modified cytokine of claim 61, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 190, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

63. (Previously presented) A modified IFNα-I cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 191 in the IFNα-I corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-I.

64. (Currently amended) The IFNα-I modified cytokine of claim 63, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 191, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

65. (Previously presented) A modified IFNα-J cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 192 in the IFNα-J corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-J.

66. (Currently amended) The IFNα-J modified cytokine of claim 65, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 192, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

67. (Previously presented) A modified IFNα-H cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 193 in the IFNα-H corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements

lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-H.

68. (Currently amended) The IFNα-H modified cytokine of claim 67, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 193, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

69. (Previously presented) An IFNα-F cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 194 in the IFNα-F corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-F.

70. (Currently amended) The IFNα-F modified cytokine of claim 69, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 194, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

71. (Previously presented) An IFNα-8 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 195 in the IFNα-8 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-8.

72. (Currently amended) The IFNα-8 modified cytokine of claim 71, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 195, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

73. (Previously presented) An IFNα-consensus cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 232 in the IFNα-consensus cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNα-consensus.

74. (Currently amended) The modified cytokine of claim 1 that is an IFNα-consensus cytokine, that is human and is selected from ~~the group consisting of~~ cytokines comprising one or more single amino acid replacements in SEQ ID NO: 232, corresponding

to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

75. (Previously presented) A modified IFNβ cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 196 in the IFNβ cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNβ.

76. (Currently amended) A modified IFNβ cytokine of claim 1, comprising mutations at one or more amino acid residues of IFNβ corresponding to SEQ ID NO:196 at positions corresponding to: 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109, 110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

77. (Currently amended) The modified IFNβ cytokine of claim 75, wherein the replacements are selected from ~~the group consisting of~~ amino acid ~~sustitutions~~substitutions in SEQ ID NO:196 corresponding to: D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q

at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

78. (Canceled)

79. (Canceled)

80. (Canceled)

81. (Canceled)

82. (Previously presented) A modified IFN-gamma cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 199 in the IFN-gamma corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFN-gamma.

83. (Currently amended) A modified cytokine of claim 4 that is an IFN-gamma cytokine, comprising mutations at one or more amino acid residues of IFN-gamma corresponding to SEQ ID NO:199 at positions 33, 37, 40, 41, 42, 58, 61, 64, 65 and 66, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

84. (Currently amended) The modified IFN-gamma cytokine of claim 82, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO:199 corresponding to:

L33V	E41Q	K58Q	D65Q
L33I	E41N	K58N	D65N
K37Q	E41H	K61Q	D66Q,
K37N	E42Q	K61N	
K40Q	E42N	K64Q	
K40N	E42H	K64N	

wherein the first amino acid listed is substituted by the second at the position indicated.

85. (Previously presented) A modified IL-10 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 200 in the IL-10 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements

lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-10.

86. (Currently amended) A modified IL-10 cytokine, comprising mutations at one or more amino acid residues of IL-10 corresponding to SEQ ID NO: 200 at positions 49, 50, 52, 53, 54, 55, 56, 57, 59, 60, 67, 68, 71, 72, 74, 75, 78, 81, 84, 85, 86, and 88, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

87. (Currently amended) The modified IL-10 cytokine of claim 85, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO:200 corresponding to:

K49Q	E54N	L60V	Y72I	E81N
K49N	E54H	L60I	E74Q	E81H
E50Q	D55Q	E67Q	E74N	D84Q
E50N	D55N	E67N	E74H	D84N
E50H	F56I	E67H	E75Q	P85S
L52V	F56V	M68V	E75N	P85A
L52I	K57Q	M68I	E75H	D86Q
L53V	K57N	F71I	P78S	D86N
L53I	Y59H	F71V	P78A	K88Q
E54Q	Y59I	Y72H	E81Q	K88N,

wherein the first amino acid listed is substituted by the second at the position indicated.

88. (Previously presented) A modified erythropoietin cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 201 in the erythropoietin corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified erythropoietin.

89. (Currently amended) A modified erythropoietin of claim 88, comprising mutations at one or more amino acid residues of erythropoietin corresponding to SEQ ID NO: 201 at positions 43, 45, 48, 49, 52, 53, 55, 72, 75, 76, 123, 129, 130, 131, 162, and 165, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

90. (Currently amended) The modified erythropoietin cytokine of claim 88, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 201 corresponding to:

D43Q	K52Q	E72N	P122S	R131H
D43N	K52N	E72H	P122A	R131Q
K45Q	R53H	L75V	D123Q	R162H
K45N	R53Q	L75I	D123N	R162Q
F48I	E55Q	R76H	P129S	D165Q
F48V	E55N	R76Q	P129A	D165N
Y49H	E55H	P121S	L130V	
Y49I	E72Q	P121A	L130I	

wherein the first amino acid listed is substituted by the second at the position indicated.

91. (Previously presented) A modified GM-CSF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 202 in the GM-CSF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified GM-CSF.

92. (Currently amended) A modified cytokine of claim 91 that is a GM-CSF cytokine, comprising mutations at one or more amino acid residues of GM-CSF corresponding to SEQ ID NO: 202 at positions 38, 41, 45, 46, 48, 49, 51, 60, 63, 67, 92, 93, 119, 120, 123, and 124, wherein the mutations <u>are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof</u>. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

93. (Currently amended) The modified GM-CSF cytokine of claim 91, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 202 corresponding to:

E38Q	D48Q	K63Q	F119V
E38N	D48N	K63N	D120Q
E38H	L49V	R67H	D120N
E41Q	L49I	R67Q	E123Q
E41N	E51Q	P92S	E123N
E41H	E51N	P92A	E123H
E45Q	E51H	E93Q	P124S
E45N	E60Q	E93N	P124A,
E45H	E60N	E93H	
M46V	E60H	F119I	

M46I

wherein the first amino acid listed is substituted by the second at the position indicated.

94. (Previously presented) A modified Flt3 ligand cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 203 in the Flt3 ligand corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokine of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified Flt3 ligand.

95. (Currently amended) A modified Flt3 ligand cytokine of claim 94, comprising mutations at one or more amino acid residues of Flt3 ligand corresponding to SEQ ID NO: 203 at positions 3, 40, 42, 43, 55, 58, 59, 61, 89, 90, 91, 95, and 96, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

96. (Currently amended) The modified Flt3 ligand cytokine of claim 94, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 203 corresponding to:

D3Q	R55Q	P89A
D3N	E58Q	P90S
D40Q	E58N	P90A
D40N	E58H	P91S
E42Q	R59H	P91A
E42N	R59Q	R95H
E42H	K61Q	R95Q
L43V	K61N	F96I
L43I	P89S	F96V,
R55H		

wherein the first amino acid listed is substituted by the second at the position indicated.

97. (Previously presented) A modified IL-2 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 204 in the IL-2 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-2.

98. (Currently amended) A modified IL-2 cytokine of claim 97, comprising mutations at one or more amino acid residues of IL-2 corresponding to SEQ ID NO: 204 at

positions 43, 45, 48, 49, 52, 53, 60, 61, 65, 67, 68, 72, 100, 103, 104, 106, 107, 109, 110, and 132, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

99. (Currently amended) The modified IL-2 cytokine of claim 97, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 204 corresponding to:

K43Q	L53I	E68Q	Y107I
K43N	E60Q	E68N	D109Q
Y45H	E60N	E68H	D109N
Y45I	E60H	L72V	E110Q
K48Q	E61Q	L72I	E110N
K48N	E61N	E100Q	E110H
K49Q	E61H	E100N	L132V
K49N	P65S	E100H	L132I
E52Q	P65A	F103I	E106Q
E52N	E67Q	F103V	E106N
E52H	E67N	M104V	E106H
L53V	E67H	M104I	Y107H,

wherein the first amino acid listed is substituted by the second at the position indicated.

100. (Previously presented) A modified IL-3 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 205 in the IL-3 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-3.

101. (Currently amended) A modified IL-3 cytokine of claim 100, comprising mutations at one or more amino acid residues of IL-3 corresponding to SEQ ID NO: 205: at positions 37, 43, 46, 59, 63, 66, 96, 100, 101, and 103, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

102. (Currently amended) The modified IL-3 cytokine of claim 100, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO:205 corresponding to:

F37I	E59Q	P96A
F37V	E59H	K100Q

E43Q	R63H	K100N
E43N	R63Q	D101Q
E43H	K66Q	D101N
D46Q	K66N	D103Q
D46N	P96S	D103N,

wherein the first amino acid listed is substituted by the second at the position indicated.

103. (Previously presented) A modified SCF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 206 in the SCF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified SCF.

104. (Currently amended) A modified SCF cytokine of claim 103, comprising mutations at one or more amino acid residues of SCF corresponding to SEQ ID NO: 206: at positions 27, 31, 34, 37, 54, 58, 61, 62, 63, 96, 98, 99, 100, 102, 103, 106, 107, 108, 109, 134, and 137; wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

105. (Currently amended) The modified SCF cytokine of claim 103, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 206 corresponding to:

M27V	D54Q	F63I	K100Q	E106H	E134N
M27I	D54N	F63V	K100N	P107S	E134H
K31Q	D58Q	K96Q	F102I	P107A	D137Q
K31N	D58N	K96N	F102V	R108H	D137N,
P34S	D61Q	L98V	K103Q	R108Q	
P34A	D61N	L98I	K103N	L109V	
D37Q	K62Q	K99Q	E106Q	L109I	
D37N	K62N	K99N	E106N	E134Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

106. (Previously presented) A modified IL-4 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 207 in the IL-4 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-4.

107. (Currently amended) A modified IL-4 cytokine of claim 106, comprising mutations at one or more amino acid residues of IL-4 corresponding to SEQ ID NO: 207: at positions 26, 37, 53, 60, 61, 64, 66, 100, 102, 103, and 126, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

108. (Currently amended) The modified IL-4 cytokine of claim 106, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 207 corresponding to:

E26Q	E60Q	L66V	E103N
E26N	E60N	L66I	E103H
E26H	E60H	P100S	K126Q
K37Q	K61Q	P100A	K126N,
K37N	K61N	K102Q	
R53H	R64H	K102N	
R53Q	R64Q	E103Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

109. (Previously presented) A modified IL-5 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 208 in the IL-5 cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-5.

110. (Currently amended) A modified IL-5 cytokine of claim 109, comprising mutations at one or more amino acid residues of IL-5 corresponding to SEQ ID NO: 208 at positions 32, 34, 39, 46, 47, 56, 84, 85, 88, 89, 90, 102, 110, and 111, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

111. (Currently amended) The modified IL-5 cytokine of claim 109, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 208 corresponding to:

R32H	E47N	E88N	E110Q
R32Q	E47H	E88H	E110N
P34S	E56Q	E89Q	E110H
P34A	E56N	E89N	W111S

K39Q	E56H	E89H	W111H,
K39N	K84Q	R90H	
E46Q	K84N	R90Q	
E46N	K85Q	E102Q	
E46H	K85N	E102N	
E47Q	E88Q	E102H	

wherein the first amino acid listed is substituted by the second at the position indicated.

112. (Previously presented) A modified IL-13 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 209 of an IL-13 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-13.

113. (Currently amended) A modified IL-13 cytokine of claim 112, comprising mutations at one or more amino acid residues of IL-13 corresponding to SEQ ID NO: 209 at positions 32, 34, 38, 48, 79, 82, 85, 86, 88, 107, 108, 110, and 111, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

114. (Currently amended) The modified IL-13 cytokine of claim 112, wherein the replacements are selected from ~~the group consisting~~ of amino acid substitutions in SEQ ID NO: 209 corresponding to:

M32V	E48H	D86N	R110H
M32I	F79I	K88Q	R110Q
W34S	F79V	K88N	F111I
W34H	L82V	R107H	F111V
L38V	L82I	R107Q	
L38I	R85H	E108Q	
E48Q	R85Q	E108N	
E48N	D86Q	E108H	

wherein the first amino acid listed is substituted by the second at the position indicated.

115. (Previously presented) A modified G-CSF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 210 in the G-CSF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified G-CSF.

116. (Currently amended) A modified G-CSF cytokine of claim 115, comprising mutations at one or more amino acid residues of G-CSF corresponding to SEQ ID NO: 210 at

positions 61, 63, 68, 72, 86, 96, 100, 101, 131, 133, 135, 147, 169, 172, and 177, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

117. (Currently amended) The modified G-CSF cytokine of claim 115, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 210 corresponding to:

W61S	F86I	E101N	F147I
W61H	F86V	E101H	F147V
P63S	E96Q	P131S	R169H
P63A	E96N	P131A	R169Q
P68S	E96H	L133V	R172H
P68A	P100S	L133I	R172Q
L72V	P100A	P135S	P177S
L72I	E101Q	P135A	P177A,

wherein the first amino acid listed is substituted by the second at the position indicated.

118. (Previously presented) A modified leptin cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 211 in the leptin corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified leptin.

119. (Currently amended) A modified leptin cytokine of claim 118, comprising mutations at one or more amino acid residues of leptin corresponding to SEQ ID NO: 211 at positions 43, 49, 99, 100, 104, 105, 107, 108, 141 and 142, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

120. (Currently amended) The modified leptin cytokine of claim 118, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 211 corresponding to:

P43S	P99A	E105Q	D108N
P43A	W100S	E105N	D141Q
L49V	W100H	E105H	D141N
L49I	L104V	L107V	L142V
P99S	L104I	L107I	L142I,
		D108Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

121. (Original) A modified CNTF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 212 in the CNTF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified CNTF.

122. (Currently amended) A modified CNTF cytokine of claim 121, comprising mutations at one or more amino acid residues of CNTF corresponding to SEQ ID NO: 212 at positions 62, 64, 66, 67, 86, 89, 92, 100, 102, 104, 131, 132, 133, 135, 136, 138, 140, 143, 148, and 151, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

123. (Currently amended) The modified CNTF cytokine of claim 121, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 212 corresponding to:

D62Q	R89Q	E131N	E138H
D62N	E92Q	E131H	D140Q
W64S	E92N	Y132H	D140N
W64H	E92H	Y132I	P143S
E66Q	P100S	K133Q	P143A
E66N	P100A	K133N	D148Q
E66H	E102Q	P135S	D148N
L67V	E102N	P135A	L151V
L67I	E102H	R136H	L151I,
L86V	D104Q	R136Q	
L86I	D104N	E138Q	
R89H	E131Q	E138N	

wherein the first amino acid listed is substituted by the second at the position indicated.

124. (Previously presented) A modified LIF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 213 in the LIF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified LIF.

125. (Currently amended) A modified LIF cytokine of claim 124, comprising mutations at one or more amino acid residues of LIF corresponding to SEQ ID NO: 213 at

positions 69, 70, 85, 99, 102, 104, 106, 109, 137, 143, 146, 148, 149, 153, 154, and 156, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

126. (Currently amended) The modified LIF cytokine of claim 124, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 213 corresponding to:

P69S	K102N	D143Q	K153N
P69A	L104V	D143N	D154Q
F70I	L104I	Y146H	D154N
F70V	P106S	Y146I	F156I
R85H	P106A	P148S	F156V
R85Q	L109V	P148A	
R99H	L109I	D149Q	
R99Q	Y137H	D149N	
K102Q	Y137I	K153Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

127. (Previously presented) A modified oncostatin M cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 214 in the oncostatin M corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified oncostatin M.

128. (Currently amended) A modified oncostatin M cytokine of claim 127, comprising mutations at one or more amino acid residues of oncostatin M corresponding to SEQ ID NO: 214 at positions 59, 60, 63, 65, 84, 87, 89, 91, 94, 97, 99, 100, 103, and 106, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

129. (Currently amended) The modified oncostatin M cytokine of claim 127, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 214 corresponding to:

E59Q	L65I	R91Q	R100Q

E59N	R84H	K94Q	L103V
E59H	R84Q	K94N	L103I
E60Q	D87Q	D97Q	E106Q
E60N	D87N	D97N	E106N
E60H	E89Q	E99Q	E106H,
R63H	E89N	E99N	
R63Q	E89H	E99H	
L65V	R91H	R100H	

wherein the first amino acid listed is substituted by the second at the position indicated.

130. (Previously presented) A modified IL-12 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 215 in the IL-12 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-12.

131. (Currently amended) A modified IL-12 cytokine of claim 130, comprising mutations at one or more amino acid residues of IL-12 corresponding to SEQ ID NO: 215 at positions 56, 61, 66, 67, 68, 70, 72, 75, 78, 79, 82, 89, 92, 93, 107, 110, 111, 115, 117, 124, 125, 127, 128, 129, and 189, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

132. (Currently amended) The modified IL-12 cytokine of claim 130, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 215 corresponding to:

K56Q	E72Q	R92H	K117Q
K56N	E72N	R92Q	K117N
E61Q	E72H	K93Q	L124V
E61N	L75V	K93N	L124I
E61H	L75I	E107Q	M125V
L66V	R78H	E107N	M125I
L66I	R78Q	E107H	P127S
E67Q	E79Q	K110Q	P127A
E67N	E79N	K110N	K128Q
E67H	E79H	M111V	K128N
L68V	F82I	M111I	R129H
L68I	F82V	E115Q	R129Q
K70Q	L89V	E115N	R189H
K70N	L89I	E115H	R189Q,

wherein the first amino acid listed is substituted by the second at the position indicated.

133. (Previously presented) A modified hGH cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 216 in the hGH corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified hGH.

134. (Currently amended) A modified hGH cytokine of claim 133, comprising mutations at one or more amino acid residues of hGH corresponding to SEQ ID NO: 216 at positions 56, 59, 64, 65, 66, 88, 92, 94, 101, 129, 130, 133, 134, 140, 143, 145, 146, 147, 183, and 186, wherein the mutations are selected from among insertions of the native amino acid residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

135. (Currently amended) The modified hGH cytokine of claim 133, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 216 corresponding to:

E56Q	E66Q	L101V	R134Q	D147N
E56N	E66N	L101I	K140Q	R183H
E56H	E66H	E129Q	K140N	R183Q
P59S	E88Q	E129N	Y143H	E186Q
P59A	E88N	E129H	Y143I	E186N
R64H	E88H	D130Q	K145Q	E186H,
R64Q	F92I	D130N	K145N	
E65Q	F92V	P133S	F146I	
E65N	R94H	P133A	F146V	
E65H	R94Q	R134H	D147Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

136. (Previously presented) A modified IL-6 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 217 in the IL-6 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IL-6.

137. (Currently amended) A modified IL-6 cytokine of claim 136, comprising mutations at one or more amino acid residues of IL-6 corresponding to SEQ ID NO: 217 at position 64, 65, 66, 68, 69, 75, 77, 92, 98, 103, 105, 108, 133, 138, 139, 140, 149, 156, 178, and 181, wherein the mutations are selected from among insertions of the native amino acid

residues, deletions of the native amino acid residues, replacements of the native amino acid residue(s) and combinations thereof. ~~comprise insertions, deletions and replacements of the native amino acid residue(s).~~

138. (Currently amended) The modified IL-6 cytokine of claim 136, wherein the replacements are selected from ~~the group consisting of~~ amino acid substitutions in SEQ ID NO: 217 corresponding to:

P64S	F73I	R103Q	D139N
P64A	F73V	E105Q	P140S
K65Q	F77I	E105N	P140A
K65N	F77V	E105H	K149Q
M66V	E92Q	E108Q	K149N
M66I	E92N	E108N	W156S
E68Q	E92H	E108H	W156H
E68N	E98Q	D133Q	R178H
E68H	E98N	D133N	R178Q
K69Q	E98H	P138S	R181H
K69N	R103H	P138A	R181Q,
		D139Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

139. (Original) The modified IFNα-2b cytokine of claim 5 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

140. (Original) The modified IFNα-2b cytokine of claim 5 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

141. (Original) The modified IFNα-2b cytokine of claim 5 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

142. (Original) The modified IFNα-2a cytokine of claim 47 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation

in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

143. (Original) The modified IFNα-2a cytokine of claim 47 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

144. (Original) The modified IFNα-2a cytokine of claim 47 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

145. (Original) The modified IFNα-c cytokine of claim 49 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

146. (Original) The modified IFNα-c cytokine of claim 49 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

147. (Original) The modified IFNα-c cytokine of claim 49 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

148. (Original) The modified IFNα-2c cytokine of claim 51 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

149. (Original) The modified IFNα-2c cytokine of claim 51 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

150. (Original) The modified IFNα-2c cytokine of claim 51 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

151. (Original) The modified IFNα-1d cytokine of claim 53 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring

residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

152. (Original) The modified IFNα-1d cytokine of claim 53 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

153. (Original) The modified IFNα-1d cytokine of claim 53 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

154. (Original) The modified IFNα-5 cytokine of claim 55 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

155. (Original) The modified IFNα-5 cytokine of claim 55 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

156. (Original) The modified IFNα-5 cytokine of claim 55 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

157. (Original) The modified IFNα-6 cytokine of claim 57 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

158. (Original) The modified IFNα-6 cytokine of claim 57 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

159. (Original) The modified IFNα-6 cytokine of claim 57 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

160. (Original) The modified IFNα-4 cytokine of claim 59 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

161. (Original) The modified IFNα-4 cytokine of claim 59 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

162. (Original) The modified IFNα-4 cytokine of claim 59 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

163. (Original) The modified IFNα-4b cytokine of claim 61 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

164. (Original) The modified IFNα-4b cytokine of claim 61 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

165. (Original) The modified IFNα-4b cytokine of claim 61 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

166. (Original) The modified IFNα-I cytokine of claim 63 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

167. (Original) The modified IFNα-I cytokine of claim 63 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

168. (Original) The modified IFNα-I cytokine of claim 63 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

169. (Original) The modified IFNα-J cytokine of claim 65 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

170. (Original) The modified IFNα-J cytokine of claim 65 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring

residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

171. (Original) The modified IFNα-J cytokine of claim 65 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

172. (Original) The modified IFNα-H cytokine of claim 67 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

173. (Original) The modified IFNα-H cytokine of claim 67 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

174. (Original) The modified IFNα-H cytokine of claim 67 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

175. (Original) The modified IFNα-F cytokine of claim 69 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

176. (Original) The modified IFNα-F cytokine of claim 69 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

177. (Original) The modified IFNα-F cytokine of claim 69 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

178. (Original) The modified IFNα-8 cytokine of claim 71 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

179. (Original) The modified IFNα-8 cytokine of claim 71 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

180. (Original) The modified IFNα-8 cytokine of claim 71 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

181. (Original) The modified IFNα consensus cytokine of claim 73 that has increased stability compared to any of the aligned cytokines, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

182. (Original) The modified IFNα consensus cytokine of claim 73 that has decreased stability compared to any of the aligned cytokines, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

183. (Original) The modified IFNα consensus cytokine of claim 73 that has increased biological activity compared to any of the aligned cytokines, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

184. (Original) The modified IFNβ cytokine of claim 75 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

185. (Original) The modified IFNβ cytokine of claim 75 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

186. (Original) The modified IFNβ cytokine of claim 75 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

187. (Original) The modified IFN β-1 cytokine of claim 78 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

188. (Original) The modified IFN β-1 cytokine of claim 78 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

189. (Original) The modified IFN β-1 cytokine of claim 78 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

190. (Original) The modified IFN β-2a cytokine of claim 80 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

191. (Original) The modified IFN β-2a cytokine of claim 80 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

192. (Original) The modified IFN β-2a cytokine of claim 80 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

193. (Original) The modified IFN-gamma cytokine of claim 82 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

194. (Original) The modified IFN-gamma cytokine of claim 82 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

195. (Original) The modified IFN-gamma cytokine of claim 82 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

196. (Original) The modified IL-10 cytokine of claim 85 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

197. (Original) The modified IL-10 cytokine of claim 85 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

198. (Original) The modified IL-10 cytokine of claim 85 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

199. (Original) The modified erythropoietin cytokine of claim 88 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by

measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

200. (Original) The modified erythropoietin cytokine of claim 88 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

201. (Original) The modified erythropoietin cytokine of claim 88 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

202. (Original) The modified GM-CSF cytokine of claim 91 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

203. (Original) The modified GM-CSF cytokine of claim 91 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

204. (Original) The modified GM-CSF cytokine of claim 91 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

205. (Original) The modified Flt3 ligand cytokine of claim 94 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

206. (Original) The modified Flt3 ligand cytokine of claim 94 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

207. (Original) The modified Flt3 ligand cytokine of claim 94 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

208. (Original) The modified IL-2 cytokine of claim 97 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

209. (Original) The modified IL-2 cytokine of claim 97 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

210. (Original) The modified IL-2 cytokine of claim 97 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

211. (Original) The modified IL-3 cytokine of claim 100 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

212. (Original) The modified IL-3 cytokine of claim 100 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

213. (Original) The modified IL-3 cytokine of claim 100 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

214. (Original) The modified SCF cytokine of claim 103 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

215. (Original) The modified SCF cytokine of claim 103 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

216. (Original) The modified SCF cytokine of claim 103 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

217. (Original) The modified IL-4 cytokine of claim 106 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

218. (Original) The modified IL-4 cytokine of claim 106 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring

residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

219. (Original) The modified IL-4 cytokine of claim 106 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

220. (Original) The modified IL-5 cytokine of claim 109 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

221. (Original) The modified IL-5 cytokine of claim 109 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

222. (Original) The modified IL-5 cytokine of claim 109 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

223. (Original) The modified IL-13 cytokine of claim 112 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

224. (Original) The modified IL-13 cytokine of claim 112 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

225. (Original) The modified IL-13 cytokine of claim 112 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

226. (Original) The modified G-CSF cytokine of claim 115 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

227. (Original) The modified G-CSF cytokine of claim 115 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

228. (Original) The modified G-CSF cytokine of claim 115 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

229. (Original) The modified leptin cytokine of claim 118 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

230. (Original) The modified leptin cytokine of claim 118 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

231. (Original) The modified leptin cytokine of claim 118 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

232. (Original) The modified CNTF cytokine of claim 121 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

233. (Original) The modified CNTF cytokine of claim 121 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

234. (Original) The modified CNTF cytokine of claim 121 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

235. (Original) The modified LIF cytokine of claim 124 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

236. (Original) The modified LIF cytokine of claim 124 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

237. (Original) The modified LIF cytokine of claim 124 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

238. (Original) The modified oncostatin M cytokine of claim 127 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

239. (Original) The modified oncostatin M cytokine of claim 127 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

240. (Original) The modified oncostatin M cytokine of claim 127 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

241. (Original) The modified IL-12 cytokine of claim 130 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

242. (Original) The modified IL-12 cytokine of claim 130 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

243. (Original) The modified IL-12 cytokine of claim 130 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

244. (Original) The modified hGH of claim 133 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

245. (Original) The modified hGH of claim 133 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

246. (Original) The modified hGH of claim 133 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

247. (Original) The modified IL-6 cytokine of claim 136 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring

residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

248. (Original) The modified IL-6 cytokine of claim 136 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

249. (Original) The modified IL-6 cytokine of claim 136 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

250. (Previously presented) A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:

(a) identifying, within a target protein or peptide or plurality thereof, one or more target amino acids, wherein:

each target amino acid is designated an *in silico*-HIT (is-HIT); and

the is-HIT target amino acids are determined by identifying structurally homologous loci between the evolving target protein and a reference protein possessing the desired activity;

(b) identifying one or more replacement amino acids, specific for each is-HIT, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;

(c) producing a population of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein each candidate LEAD protein contains a single amino acid replacement, and wherein each polynucleotide in a set encodes a candidate LEAD protein that differs by one amino acid from the target protein or peptide;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are present in an addressable array; and

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such protein is designated a LEAD mutant protein;

251. (Original) The method of claim 250, wherein the predetermined property or activity of the evolved modified protein is increased resistance to proteolysis.

252. (Original) The method of claim 250, wherein the target proteins comprise a family.

253. (Original) The method of claim 250, wherein target proteins are cytokines.

254. (Currently amended) The method of claim 253, wherein the cytokines are selected from ~~the group consisting of~~ interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha (IFNα), interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

255. (Original) The method of claim 250, wherein each candidate lead is individually prepared and screened to identify leads.

256. (Original) The method of claim 250, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids, or the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

257. (Original) The method of claim 250, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

258. (Original) The method of claim 250, further comprising:

(f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

259. (Previously presented) The method of claim 258, wherein the nucleic acid molecules in step (g) are generated by a method selected from among additive directional mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

260. (Previously presented) The method of claim 250, wherein candidate LEADS are produced by replacing to a restricted subset of amino acids along the full length of a target protein.

261. (Original) The method of claim 250, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

262. (Original) The method of claim 250, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

263. (Original) The method of claim 258, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

264. (Previously presented) The method of claim 258, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

265. (Original) The method of claim 250, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% compared to the activity of the unmodified target protein.

266. (Previously presented) The method of claim 250, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% compared to the activity of the unmodified target protein.

267. (Original) The method of claim 250, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater than the activity of the unmodified target protein.

268. (Previously presented) The method of claim 250, wherein the replacing amino acids are selected using Percent Accepted Mutation (PAM) matrices.

269. (Original) The method of claim 250, wherein the replacing amino acids are pseudo-wild type amino acids.

270. (Original) The method of claim 250, wherein identification of the structurally homologous loci between the evolving target protein and a reference protein possessing the desired activity, comprises:

(a) comparing the 3-dimensional structures of the two or more proteins to identify regions of high coincidence between their backbones, said regions designated as structurally homologous regions; and

(b) identifying is-HIT structurally homologous loci on the evolving protein that correspond to structurally related is-HIT amino acid positions within a structurally homologous region of the reference protein.

271. (Previously presented) The method of claim 270, wherein the comparison of the 3-dimensional structures of the evolving target protein and the reference protein is based upon their 3-dimensional structures not upon alignment between their respective primary sequences.

272. (Original) The method of claim 270, wherein the evolving target protein and the reference protein belong to a family of sequence-related proteins.

273. (Previously presented) The method of claim 270, wherein the evolving target protein and the reference protein are non-related proteins or sequence-non-related proteins.

274. (Original) The method of claim 270, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and the reference protein is in a region selected from the group consisting of:

(a) a small region on the two proteins;

(b) a large region on the two proteins; and

(c) a region that covers the full length of one or both of the proteins.

275. (Original) The method of claim 270, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and of the reference protein is determined by superposition and RMS deviation calculations using any combination of one or more of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA.

276. (Original) The method of claim 275, wherein the superposition and RMS deviation calculations are made using all of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA, when present.

277. (Original) The method of claim 275, wherein the superposition and RMS deviation calculations are carried out on a subset of regions or domains of a larger protein that adopts a structure similar to a smaller protein.

278. (Previously presented) The method of claim 275, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and the reference protein is obtained using any combination of one or more of either Class Architecture, Topology and Homologous Superfamily (CATH); Combinatorial Extension of the optimal path (CE); Fold Classification based on Structure-Structure Alignment of Proteins (FSSP); Structural Classification of Proteins (SCOP); Vector Alignment Search Tool (VAST), and TOP.

279. (Previously presented) A modified cytokine of claim 1 selected from the group consisting of modified cytokines comprising a sequence of amino acids set forth in any of SEQ ID NOS: 2-181, 233-1303 or a structural homolog thereof.

280. (Currently amended) The modified cytokine of claim 279, selected from ~~the group consisting of~~ interleukin-10 (IL-10), interferon α, interferon β, interferon γ, granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

281. (Previously presented) A method of generating a modified protein or cytokine having a pre-selected altered phenotype, comprising:

modifying a first protein or cytokine by a directed evolution method to produce an evolved protein or cytokine that has the altered phenotype to identify altered loci;

comparing the structures of one or more members of the protein or cytokine family to identify structurally homologous loci for alteration; and

altering the identified loci in members of the protein or cytokine family to produce proteins or cytokines that have the altered phenotype.

282. (Original) The method of claim 281, wherein directed evolution is effected by a rational directed evolution method.

283. (Original) The method of claim 281, wherein directed evolution is effected by a 2-dimensional rational scanning.

284. (Original) The method of claim 281, wherein identification of the structurally homologous loci between the evolved protein or cytokine and members of the protein or cytokine family, further comprises:

(a) comparing the 3-dimensional structures of the evolved protein or cytokine with one or more members of the protein or cytokine family to identify regions of high coincidence between their backbones, said regions designated as structurally homologous regions; and

(b) identifying is-HIT structurally homologous loci on the members of the protein or cytokine family that correspond to structurally related is-HIT amino acid positions within a structurally homologous region of the evolved protein or cytokine.

285. (Original) The method of claim 284, wherein the comparison of the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is made irrespective of any alignment between their respective sequences.

286. (Currently amended) The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is in a region selected from ~~the group consisting of~~:

(a) a small region on the two proteins;

(b) a large region on the two proteins; and

(c) a region that covers the full length of one or both of the proteins.

287. (Currently amended) The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and of the evolved protein or cytokine is determined by superposition and RMS deviation calculations using any combination of one or more of the peptide backbone atoms selected from ~~the group consisting of~~: N, C, C(C=O), O and CA.

288. (Currently amended) The method of claim 287, wherein the superposition and RMS deviation calculations are made using all of the peptide backbone atoms present selected from ~~the group consisting of~~: N, C, C(C=O), O and CA.

289. (Original) The method of claim 287, wherein the superposition and RMS deviation calculations are carried out on a subset of regions or domains of a larger protein that adopts a structure similar to a smaller protein.

290. (Previously presented) The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is obtained using any combination of one or more of either CATH (Class Architecture, Topology and Homologous Superfamily); CE (Combinatorial Extension of the optimal path); FSSP (Fold Classification based on Structure-Structure Alignment of Proteins); SCOP (Structural Classification of Proteins); VAST (Vector Alignment Search Tool), and TOP.

291. (Previously presented) The method of claim 283, wherein the 2-dimensional rational scanning method comprises:

(a) identifying, within the first protein or cytokine, one or more target amino acids amenable to providing the altered phenotype upon amino acid replacement, wherein each target amino acid is designated an *in silico*-HIT (is-HIT);

(b) identifying one or more replacement amino acids, specific for each is-HIT, amenable to providing the altered phenotype upon amino acid replacement, wherein each single amino acid replacement within the protein or cytokine is designated as a candidate LEAD protein;

(c) producing a population of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein each candidate LEAD protein comprises a single

amino acid replacement, and wherein each polynucleotide in a set encodes a candidate LEAD protein that differs by one amino acid from the unmodified protein or cytokine;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are present in an addressable array; and

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more candidate LEAD proteins that has activity that differs from the unmodified protein or cytokine, wherein each such protein is designated a LEAD mutant protein.

292. (Original) The method of claim 291, wherein the array comprises a solid support with wells; and each well contains one set of cells.

293. (Original) The method of claim 291, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids.

294. (Original) The method of claim 291, wherein the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

295. (Original) The method of claim 291, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

296. (Original) The method of claim 291, further comprising:

(f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified protein or cytokine and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

297. (Original) The method of claim 296, wherein the nucleic acid molecules in step (f) are produced by a method selected from among Additive Directional Mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

298. (Original) The method of claim 291, wherein the is-HITs identified in step (a) correspond to a restricted subset of amino acids along the full length target protein.

299. (Original) The method of claim 291, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

300. (Original) The method of claim 291, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

301. (Original) The method of claim 296, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

302. (Previously presented) The method of claim 296, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified protein or cytokine.

303. (Original) The method of claim 291, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the activity of the unmodified target protein.

304. (Previously presented) The method of claim 291, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the activity of the unmodified target protein.

305. (Original) The method of claim 291, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater or less than the activity of the unmodified target protein.

306. (Currently amended) A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, IFN-2c cytokine selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements corresponding to the replacement of: N by D at position 45; D by G at position 94; G by R at position 102; A by G at position 139; or any combination thereof.

307. (Currently amended) A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, IFNα-2c cytokine selected from ~~selected from the group consisting of~~ proteins comprising one or more single amino acid replacements in any of SEQ ID NOS: 1, 182, 185 or 232 or any combination thereof corresponding to the replacement: L by V at position 3; L by I at position 3; P by S at position 4; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at

position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165 or any combination thereof, wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

308. (Currently amended) A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, IFNα-2c cytokine selected from ~~selected from the group consisting of~~ proteins comprising one or more single amino acid replacements in any of SEQ ID NOS: 1, 182, 185 or 232 or any combination thereof corresponding to the replacement L by V at position 3; L by I at position 3; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I

at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; E by H at position 165; N by D at position 45; D by G at position 94; G by R at position 102; and A by G at position 139, wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS: 1 or 182.

309. (Original) The modified cytokine of claim 1, that is an interferon β (IFNβ).

310. (Currently amended) A modified IFN β cytokine of claim 309 selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements in SEQ ID NO:196, corresponding to the replacement of M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at

position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at

position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at

position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90,

wherein residue 1 corresponds to residue 1 of the mature IFNβ cytokine set forth in SEQ ID NO:196.

311. (Original) A modified cytokine of claim 1 that comprises one or more pseudo-wild type mutations.

312. (Original) The modified cytokine of claim 311 that is a modified IFNβ.

313. (Original) A modified IFNβ cytokine of claim 309 that has increased antiviral activity compared to the unmodified cytokine.

314. (Previously presented) The modified IFNβ cytokine of claim 313, wherein antiviral activity is assessed by measuring replication by reverse transcription quantification PCR (RT-qPCR) or CPE (cytopathic effect).

315. (Currently amended) A modified IFNα-2b or IFNα-2a cytokine of claim 308 that has more antiviral activity than anti-proliferative activity compared to the unmodified cytokine.

316. (Currently amended) The cytokine of claim 315, wherein anti-proliferative activity is assessed by measuring cell proliferation in the presence of the cytokine.

317. (Currently amended) A modified IFNβ cytokine of claim 309 that binds to an IFN receptor, but exhibits when compared to unmodified IFNβ, decreased antiviral activity and decreased anti-proliferative activity relative to its receptor binding activity.

318. (Original) A modified cytokine of claim 1, comprising two or more mutations.

319. (Original) A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

320. (Original) A modified cytokine that exhibits greater resistance to proteolysis compared to the unmodified cytokine, comprising one or more amino acid replacements at one or more target positions on the cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNβ modified cytokines of claim 309.

321. (Currently amended) A modified cytokine of claim 320, wherein the resistance to proteolysis is measured by ~~mixing it~~ mixture with a protease *in vitro*, incubation with blood or incubation with serum.

322. (Original) A cytokine structural homolog of an IFNβ modified cytokine of claim 309, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of the modified IFNβ.

323. (Original) A cytokine homolog of claim 322, wherein the homolog has increased resistance to proteolysis compared to its unmodified cytokine counterpart, wherein the resistance to proteolysis is measured by mixture with a protease *in vitro*, incubation with blood, or incubation with serum.

324. (Previously presented) A modified IFNβ cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO. 196 in the IFNβ corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNβ modified cytokines of claim 309, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or with a blood lysate or by incubation with serum, compared to the unmodified IFNβ.

325. (Original) The modified IFNβ cytokine of claim 309 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

326. (Original) The modified IFNβ cytokine of claim 309 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

327. (Original) The modified IFNβ cytokine of claim 309 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

328. (Currently amended) A modified of IFNβ cytokine of claim 309, selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements in SEQ ID NO:196, or any combination thereof, corresponding to the replacement of: M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q

position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at

position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at

position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90,

wherein residue 1 corresponds to residue 1 of the mature IFNβ cytokine set forth in SEQ ID NO:196.

329. (Currently amended) A modified IFNβ cytokine of claim 309 selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements in SEQ ID NO:196, or any combination thereof, corresponding to the replacement of: D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by

S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

330. (Currently amended) A modified IFNβ cytokine of claim 309 selected from ~~the group consisting of~~ proteins comprising one or more single amino acid replacements in SEQ ID NO:196, or any combination thereof, corresponding to the replacement of: M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at

position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at

position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by

Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

331. (Currently amended) A modified IFNβ of claim 330 selected from ~~the group consisting of~~ a modified IFNβ set forth in any of SEQ ID NOS: 234-289, 989-1302.

AMENDMENTS TO THE FIGURES:

Please replace Figure 9 in the above-captioned application with the attached replacement Figure 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. Applicants submit that no new matter has been added to the drawing.

AMENDMENTS TO THE SEQUENCE LISTING:

Please replace the Sequence Listing in the above-captioned application with the attached substitute Sequence Listing. Annotated substitute sheets of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, 1043, and 1306 are included herein to point out the amendments made herein to the sequence listing. Applicants assert that the application is in compliance with 37 C.F.R. §§ 1.821-1.825 and that no new matter has been added.

REMARKS

Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

IN THE SPECIFICATION:

Amendments to the specification include amendments to the Description of the Figures to bring the specification into compliance with the Sequence Rules set forth in 37 C.F.R. §§ 1.821-1.825. Additional amendments seek to correct inadvertent errors in references to SEQ ID NO identifiers used in the specification. Further amendments correct minor errors to produce grammatical clarity.

Amendments to pages 11-14 incorporate SEQ ID NO identifiers to the Description of the Figures to correctly reference the Sequence Listing in compliance with the Sequence Rules set forth in 37 C.F.R. §§ 1.821-1.825. In addition, the Description of the Figures also have been amended to specify the particular residues of the respective protein sequence referenced within the Figures as compared to the sequences provided in the Sequence Listing. These amendments find basis in the Figures as originally filed (and in the case of Figure 9, *as amended herein*) and in the Sequence Listing as originally filed (and in the case of IL-10 (SEQ ID NO: 200), SCF (SEQ ID NO: 206), and Flt3 ligand (SEQ ID NO: 203), *as amended herein*). For example, the amendment to the paragraph beginning on page 11, line 11 incorporates the SEQ ID NO identifiers for the sequences for IFN-α2b, IFNβ, EPO, and G-CSF described in FIG. 9 of the drawings.

Amendments to the paragraph beginning on page 11, line 29 incorporates the SEQ ID NO identifiers 989-1015 and 1016-1302 of the Sequence Listing which, in addition to the SEQ ID NO identifiers 233-289 already listed, provide a complete listing of all of the modified protein sequences of interferon β represented in the Sequence Listing. In addition, the paragraph on page 11, line 29 also is amended to recite "a representative number of" in order to correctly reflect that the listed substitutions 1-57 in FIG. 12A are not the only modified interferon β is-HITs, but rather are representative of modified interferon β sequences as specified by SEQ ID NOS: 233-289, 989-1015, and 1016-1302. Basis for this amendment can be found in the specification at page 99, line 1 through page 112, line 31 which lists the is-HIT target positions on IFNβ, based on the mature protein sequence of

IFNB depicted by SEQ ID NO: 196. Amendments to the paragraph beginning on page 11, line 29 also incorporates the SEQ ID NO identifier for the wild-type sequence of Interferon β depicted in Fig. 12A and specified by SEQ ID NO:196.

Amendments to the paragraph beginning on page 12, line 3 incorporates the SEQ ID NO identifier for the wild-type sequence of interferon gamma and specifies the residues of the interferon gamma sequence depicted in Fig. 12B as specified by SEQ ID NO: 199. Amendments to the paragraph beginning on page 12, line 7 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-10 and specifies the residues of the interleukin-10 sequence depicted in Fig. 12C as specified by SEQ ID NO: 200 *as amended herein*. Amendments to the paragraph beginning on page 12, line 11 incorporates the SEQ ID NO identifier for the wild-type sequence of ciliary neurotrophic factor and specifies the residues of the ciliary neurotrophic factor sequence depicted in Fig. 12D as specified by SEQ ID NO:212. Amendments to the paragraph beginning on page 12, line 15 incorporates the SEQ ID NO identifier for the wild-type sequence of granulocyte-colony stimulating factor and specifies the residues of the granulocyte-colony stimulating factor sequence depicted in Fig. 12E as specified by SEQ ID NO:210. Amendments to the paragraph beginning on page 12, line 19 incorporates the SEQ ID NO identifier for the wild-type sequence of human growth hormone and specifies the residues of the human growth hormone sequence depicted in Fig. 12F as specified by SEQ ID NO:216. Amendments to the paragraph beginning on page 12, line 23 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-12 and specifies the residues of the interleukin-12 sequence depicted in Fig. 12G as specified by SEQ ID NO:215. Amendments to the paragraph beginning on page 12, line 27 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-6 and specifies the residues of the interleukin-6 sequence depicted in Fig. 12H as specified by SEQ ID NO:217. Amendments to the paragraph beginning on page 13, line 1 incorporates the SEQ ID NO identifier for the wild-type sequence of leptin as depicted in Fig. 12I and specified by SEQ ID NO:211. Amendments to the paragraph beginning on page 13, line 5 incorporates the SEQ ID NO identifier for the wild-type sequence of leukemia inhibitory factor and specifies the residues of the leukemia inhibitory factor sequence depicted in Fig. 12J as specified by SEQ ID NO:213. Amendments to the paragraph beginning on page 13, line 9 incorporates the SEQ ID NO identifier for the wild-type sequence of oncostatin M and

specifies the residues of the oncostatin M sequence depicted in Fig. 12K and specified by SEQ ID NO:214. Amendments to the paragraph beginning on page 13, line 13 incorporates the SEQ ID NO identifier for the wild-type sequence of erythropoietin as depicted in Fig. 12L and specified by SEQ ID NO:201. Amendments to the paragraph beginning on page 13, line 17 incorporates the SEQ ID NO identifier for the wild-type sequence of Flt3 ligand and specifies the residues of the Flt3 ligand sequence depicted in Fig. 12M as specified by SEQ ID NO:203 *as amended herein*. Amendments to the paragraph beginning on page 13, line 21 incorporates the SEQ ID NO identifier for the wild-type sequence of granulocyte-macrophage colony-stimulating factor as depicted in Fig. 12N and specified by SEQ ID NO:202. Amendments to the paragraph beginning on page 13, line 25 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-13 as depicted in Fig. 12O and specified by SEQ ID NO:209. Amendments to the paragraph beginning on page 13, line 29 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-2 as depicted in Fig. 12P and specified by SEQ ID NO:204. Amendments to the paragraph beginning on page 14, line 3 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-3 as depicted in Fig. 12Q and specified by SEQ ID NO:205. Amendments to the paragraph beginning on page 14, line 7 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-4 as depicted in Fig. 12R and specified by SEQ ID NO:207. Amendments to the paragraph beginning on page 14, line 11 incorporates the SEQ ID NO identifier for the wild-type sequence of interleukin-5 as depicted in Fig. 12S and specified by SEQ ID NO: 208. Amendments to the paragraph beginning on page 14, line 15 incorporates the SEQ ID NO identifier for the wild-type sequence of stem cell factor and specifies the residues of the stem cell factor sequence depicted in Fig. 12T as specified by SEQ ID NO:206 *as amended herein*.

Amendment to the paragraph on page 61, line 8-9 moves the position of the SEQ ID NO identifier (SEQ ID NO:1) in the sentence to improve clarity. SEQ ID NO:1 is the sequence identifier for the amino acid sequence of IFNα-2b which finds basis at page 1 of the Sequence Listing and throughout the specification, such as at page 69, lines 9-10. Since the amended sentence at page 61, lines 8-9 refers to both the mature peptide IFNα-2b and the nucleotides which encode that peptide, the SEQ ID NO:1 has been moved so that it is clear that the identifier refers to the protein sequence and not the nucleotide sequence of IFNα-2b.

No new matter has been added to the specification.

IN THE CLAIMS:

Claims 1-77 and 82-331 are pending in this application. Claims 78-81 are canceled herein without prejudice or disclaimer. Applicants reserve the right to prosecute any canceled subject matter in a continuing application. Claims 2, 3, 6-9, 12, 14, 15, 18-20, 24, 33, 41-43, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 77, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, 123, 125, 126, 128, 129, 131, 132, 134, 135, 137, 138, 254, 280, 286-288, 306-308, 310, 315-317, 321, 328-331 are amended herein. Support for the amendments to claims 76, 83, 86, 89, 92, 95, 98, 101, 104, 107, 113, 116, 119, 122, 125, 128, 131, 134 and 137 can be found throughout the specification as filed. See, for example, lines 20-24 of page 35, lines 10-15 of page 74 and lines 1-5 of page 75 of the specification. All other claims are amended to correct grammatical errors and do not alter the substance of the claims.

No new matter has been added to the claims.

IN THE FIGURES:

Attached herewith is a replacement drawing of Fig. 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. Amendments to the Figures include amendments to Fig. 9 to correct the sequence of G-CSF depicted within Fig. 9. The sequence of G-CSF depicted in Fig. 9 inadvertently is missing several amino acid residues. Fig. 9 is amended herein to correct these inadvertent errors by amending the sequence to add in the first three amino acids, Thr Pro Leu (TPL), of the mature protein sequence and also to add three amino acids, Val Ser Glu (VSE), corresponding to position 36-38 of the wild-type sequence of G-CSF as depicted in SEQ ID NO: 210 of the Sequence Listing. Basis for this amendment can be found within SEQ ID NO: 210 of the Sequence Listing as originally filed. SEQ ID NO: 210 is described in the specification at page 6, line 2 as granulocyte colony stimulating factor (G-CSF). As further support for the amendment, the sequences of the other cytokines depicted within Fig. 9, (e.g., IFN-α2b, IFN-β, and EPO) are the exact wild-type sequences of the respective cytokines as specified in the Sequence Listing and pertain to SEQ ID NOS: 1, 196, and 201, respectively.

No new matter has been added to the Figures.

IN THE SEQUENCE LISTING:

Attached herewith are a substitute Sequence Listing, marked-up paper copies of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, and 1043 indicating the changes made, and a verified statement that the content of the computer-readable copy and the substitute Sequence Listing are the same in accordance with 37 C.F.R. §§1.821-1.825.

Amendments to the Sequence Listing include amendments at page 99 of the Sequence Listing to correct a typographical error in the Numeric identifier (<308>) of SEQ ID NO: 200. The database accession number was inadvertently listed as "Genbank NP_00063" and is amended herein to be "Genbank NP_000563." Basis for this amendment can be found within the specification at page 5, line 29 where SEQ ID NO: 200 is described as interleukin-10. One of ordinary skill in the art would recognize that Genbank NP_00063 is obviously incorrect as it is not a complete accession number, whereas Genbank NP_000563 is a complete accession number that correctly identifies the sequence of the interleukin 10 (IL-10) precursor sequence including the mature protein sequence representing amino acids 19-178 of the precursor IL-10. Further, although the database entry date (<309>) of 2000-10-31 in the sequence listing for Genbank NP_000563 has changed to 2005-06-21, a person of ordinary skill in the art would recognize that the sequence for IL-10 listed in Genbank NP_000563 is not different from earlier known sequences for IL-10. For instance, in the "Comment" section of the entry data for Genbank NP_000563 it states that "the reference sequence was derived from M57627.1 and BC022315.1". Genbank M57627.1 is the nucleotide sequence for IL-10 with a database entry date of 1995-03-07 and links to Genbank AAA63207 which is the protein sequence of IL-10 also with an entry date also of 1995-03-07. The database accession numbers NP_000563 and AAA63207 depict the exact same sequence for a precursor IL-10 protein of 178 amino acids and a mature protein sequence representing amino acids 19-178 of the precursor IL-10. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at line 29 of page 5 and the Sequence Listing at page 99 with respect to IL-10, Applicant intent at the time of filing was to reference the Genbank NP_000563 sequence. Therefore, the correction of the typographical error in the Genbank identifier does not introduce new matter.

The Numeric identifier (<308>) of SEQ ID NO: 206 on page 101 of the Sequence Listing also is amended herein to correct a typographical error. The database accession number was inadvertently listed as "Genbank AAA85480" and is amended herein to be "Genbank AAA85450." Basis for this amendment can be found within the specification at page 6, line 12 where SEQ ID NO: 206 is described as stem cell factor (SCF). One of ordinary skill in the art would recognize that Genbank AAA85480 is obviously incorrect as this references a bacterial gene product of 17 amino acids, whereas Genbank AAA85450 correctly identifies the sequence of the SCF precursor sequence including the mature protein sequence representing amino acids 26-273 of the precursor SCF. Further, the database entry date (<309>) of 1996-01-19 listed in the sequence listing for Genbank AAA85450 has not changed. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at line 12 of page 6 and the Sequence Listing at page 101 with respect to stem cell factor, Applicant intent at the time of filing was to reference the Genbank AAA85450 sequence. Therefore, the correction of the typographical error in the Genbank identifier does not introduce new matter.

SEQ ID NO. 200 at page 99 of the Sequence Listing and SEQ ID NOS: 312-361 on pages 143-159 of the Sequence Listing are amended to provide the full-length sequence corresponding to the mature IL-10 protein having 160 amino acids by adding the final 60 amino acids to the sequences. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 200 and 312-361 provided herewith. Basis for this amendment can be found in the specification, at lines 14-20 of page 90,where SEQ ID NO: 200 is described in the specification as IL-10 and SEQ ID NOS: 312-361 are described as IL-10 sequences containing substitutions of the native amino acid sequence. Further support for this amendment can be found in the Sequence Listing on page 99, *as amended herein*, where the numeric identifier "<308>" specifies the Database Accession number as being "Genbank NP_000563." Genbank number NP_000563 sets forth an Interleukin 10 precursor protein wherein the mature protein is represented by amino acids 19-178 of the sequence, thereby designating a mature protein of 160 amino acids in length. Further, as discussed above, although the database entry date (<309>) of 2000-10-31 listed in the sequence listing for Genbank NP_000563 has changed, one of ordinary skill in the art would recognize that the sequence for IL-10 listed in Genbank NP_000563 is not different from earlier known

sequences for IL-10. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at lines 14-20 of page 90 and of the Sequence Listing at page 99, that the mature (native) amino acid sequence of the IL-10 amino acid sequence provided in Genbank NP_000563 was the intended sequence. Therefore, the addition of the last 60 amino acids to the sequences of SEQ ID NOS: 200 and 312-361 does not introduce new matter, but rather corrects the sequences to correspond to the complete mature protein sequence of 160 amino acids.

SEQ ID NO. 203 at page 100 of the Sequence Listing and SEQ ID NOS: 401-428 at pages 173-182 of the Sequence Listing are amended to provide the full-length sequence corresponding to the mature Flt3 ligand protein having 209 amino acids by adding the final 109 amino acids to the sequences. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 203 and 401-428 provided herewith. Basis for this amendment can be found in the specification, at lines 5-11 of page 91, where SEQ ID NO: 203 is described in the specification as Flt3 ligand and SEQ ID NOS: 401-428 are described as Flt3 ligand sequences containing substitutions of the native amino acid sequence. Further support for this amendment can be found in the Sequence Listing on page 100 where the numeric identifier "<308>" specifies the Database Accession number as being "Genbank AAA19825." Genbank number AAA19825 sets forth a Flt3 ligand precursor protein wherein the mature protein is represented by amino acids 27-235 of the sequence, thereby designating a mature protein of 209 amino acids in length. Further, the database entry date (<309>) of 1994-07-19 listed in the sequence listing for Genbank AAA19825 has not changed. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at lines 5-11 of page 91 and of the Sequence Listing at page 100, that the mature (native) amino acid sequence of the Flt3 ligand amino acid sequence provided in Genbank AAA19825 was the intended sequence. Therefore, the addition of the last 109 amino acids to the sequences of SEQ ID NOS: 203 and 401-428 does not introduce new matter, but rather corrects the sequences to correspond to the complete mature protein sequence of 209 amino acids.

SEQ ID NO. 206 at page 101-102 of the Sequence Listing and SEQ ID NOS: 499-542 on pages 209-226 of the Sequence Listing are amended to provide the full-length sequence corresponding to the mature stem cell factor (SCF) protein having 248 amino acids by adding

the final 107 amino acids to the sequences. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 206 and 499-542 provided herewith. Basis for this amendment can be found in the specification, at line 27 of page 91 through line 3 of page 92, where SEQ ID NO: 206 is described in the specification as SCF and SEQ ID NOS: 499-542 are described as SCF sequences containing substitutions of the native amino acid sequence. Further support for this amendment can be found in the Sequence Listing on page 101, *as amended herein*, where the numeric identifier "<308>" specifies the Database Accession number as being "Genbank AAA85450." Genbank number AAA85450 sets forth a SCF precursor protein wherein the mature protein is represented by amino acids 26-273 of the sequence, thereby designating a mature protein of 248 amino acids in length. Further, the database entry date (<309>) of 1996-01-19 listed in the sequence listing for Genbank AAA85450 has not changed. Thus, one of ordinary skill in the art would recognize, in view of the disclosure of the specification at line 27 of page 91, through line 3 of page 92 and of the Sequence Listing at page 101, that the mature (native) amino acid sequence of the SCF sequence provided in Genbank AAA85450 was the intended sequence. Therefore, the addition of the last 107 amino acids to the sequences of SEQ ID NOS: 206 and 499-542 does not introduce new matter, but rather corrects the sequences to correspond to the complete mature protein sequence of 248 amino acids.

As further support for these amendments, other cytokines included in the Sequence Listing contain the same number of amino acids as represented by the mature protein as specified by the respective Genbank numeric identifier. For example, SEQ ID NO: 210, which sets forth the sequence of the mature G-CSF protein, specifies the numeric identifier (<308>) "Genbank CAA27168" at page 103 of the Sequence Listing and specifies the database entry date (<309>) of 1995-03-21. One of ordinary skill in the art would recognize that Genbank CAA27168, with an entry date of 1995-03-21, designates a G-CSF protein of 207 amino acids, whereby amino acids 1-30 represent the signal sequence and amino acids 31-207 represent the mature protein of 177 amino acids as set forth exactly in SEQ ID NO:210. The modified sequences of G-CSF corresponding to SEQ ID NOS: 631-662 also set forth a sequence of 177 amino acids which are described in the specification at page 92, lines 25-31 as being sequences comprising mutations of one or more amino acid residues of G-CSF set forth in SEQ ID NO:210.

SEQ ID NOS: 290-311 on pages 136-143 of the Sequence Listing are amended herein to add the final 46 amino acids of the mature protein of Interferon gamma as set forth in SEQ ID NO: 199 at pages 98-99 of the Sequence Listing. These amino acids were inadvertently omitted from SEQ ID NOS: 290-311, but are contained in the reference wild-type sequence of Interferon gamma depicted in SEQ ID NO: 199. For reference, these changes are underlined on the paper copies of SEQ ID NOS: 290-311 provided herewith. Basis for these amendments can be found in the specification, at lines 7-13 of page 90, where SEQ ID NO: 199 is described in the specification as Interferon gamma and SEQ ID NOS: 290-311 are described as modified Interferon gamma cytokines comprising mutations of one or more amino acid residues of Interferon gamma corresponding to amino acid substitutions in SEQ ID NO: 199. Thus, the sequences of SEQ ID NOS: 290-311 should be identical to the sequence of SEQ ID NO: 199 *except* for the point mutations at the positions listed on page 90 of the specification (*e.g.* 33, 37, 40, 41, 42, 58, 61, 64, 65, and 66). These substitutions are described in Fig. 12B as substitutions 1 through 21. Therefore, the addition of the last 46 amino acids to the sequences of SEQ ID NOS; 290-311 does not introduce new matter, but rather corrects the modified sequences of SEQ ID NOS: 290-311 to correspond to the reference wild-type sequence of Interferon gamma (SEQ ID NO: 199).

As further support for this amendment, other modified sequences in the Sequence Listing correspond exactly to their reference wild-type sequence *except* for point mutations introduced into the sequence at one or more amino acid position. For example, as described in the specification at lines 25-31 of page 92, and in the Sequence Listing at pages 103 and 257-272, SEQ ID NO: 210, which sets forth the 177 amino acid sequence for the mature protein G-CSF, is identical to the modified sequences of G-CSF corresponding to SEQ ID NOS: 631-662 *except* for the amino acid positions containing mutations.

SEQ ID NO: 1043 on page 454 of the Sequence Listing is amended to correct a typographical error whereby the sequence only listed 165 amino acids because the amino acid at position 166 was inadvertently omitted. Amino acid 166 has been added herein by amendment to be Asparagine (Asn). For reference, this change is underlined on the paper copy of SEQ ID NO: 1043 provided herewith. Basis for this amendment can be found in the specification at line 1 of page 99 through line 31 of page 112, where SEQ ID NO: 1043 is described as one of the modified Interferon beta cytokines comprising mutations of one or

more amino acid residues of Interferon beta corresponding to amino acid substitutions in SEQ ID NO: 196. Thus, the sequence of SEQ ID NO:1043 should be identical to the sequence of SEQ ID NO: 196 *except* for a point mutation at one of the positions listed on pages 99-112 of the specification. In the case of SEQ ID NO:1043, the point mutation is at amino acid position 22 where, compared to the reference SEQ ID NO:196 (*i.e.*, the mature wild-type sequence), the amino acid at position 22 has been changed from Tryptophan (W) to Histidine (H). Therefore, the addition of the last amino acid at position 166 to the sequence of SEQ ID NO: 1043 does not introduce new matter, but rather corrects the modified sequences of SEQ ID NO: 1043 to correspond to the reference wild-type sequence of Interferon beta (SEQ ID NO: 196).

In the preliminary amendment filed April 29, 2004, it was stated at page 4, lines 1-4 that "SEQ ID NO: 978 on page 523 and SEQ ID NO: 986 on page 528 of the Sequence Listing are amended to correct inadvertent typographical errors introduced in the sequence at amino acid position 158. Amino acid 158 is amended to Glycine (Gln) to replace Proline (Pro) in each of these sequences."

Amino acid 158 was amended to Gln to replace Pro as evidenced by the Sequence Listing. Applicant notes that it is well-known in the art that "Gln" is the three-letter abbreviation for Glutamine, not Glycine (Gly) such as disclosed in Table 1 of the specification. No changes have been made to SEQ ID NOS: 978 and 986.

In addition, the Title of Invention as specified by the <120> numeric identifier has been changed to reflect the correct title of the invention. This correction finds basis on the first page of the specification where the correct title of the invention is shown to be "Rational Evolution of Cytokines for Higher Stability, the Cytokines and Encoding Nucleic Acid Molecules."

No new matter has been added to the Sequence Listing.

The computer-readable copy of the Sequence Listing is entitled 922SEQ.004 and is identical to the substitute Sequence Listing. The replacement Sequence Listing does not contain new matter.

No new matter is made to any of the amendments to the specification, Claims, Figures, or Sequence Listing. Entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,

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Reg. No. 33,779

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email: seidman@fr.com

APPENDIX
Attached herewith are:

1. Annotated paper copies of SEQ ID NOS: 200, 203, 206, 290-311, 312-361, 401-428, 499-542, 1043;
2. Substitute Sequence Listing;
3. Computer-readable copy of substitute Sequence Listing;
3. Verified Statement Pursuant to §1.821(f); and
4. Replacement Sheet of Fig. 9 Pursuant to §1.84.

<210> 200
<211> 160
<212> PRT
<213> Homo sapiens

<300>
<308> Genbank NP_00063
<309> 2000-10-31

<400> 200

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Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 203
<211> 209
<212> PRT
<213> Homo sapiens

<300>
<308> Genbank AAA19825
<309> 1994-07-19

<400> 203

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Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
```

<212> PRT
<213> Homo sapiens

<400> 290
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
1 5 10 15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
20 25 30
Val Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
35 40 45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
50 55 60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65 70 75 80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
85 90 95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
100 105 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
115 120 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
130 135 140
Ser Gln
145

<210> 291
<211> 146
<212> PRT
<213> Homo sapiens

<400> 291
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
1 5 10 15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
20 25 30
Ile Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
35 40 45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
50 55 60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65 70 75 80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
85 90 95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
100 105 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
115 120 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
130 135 140
Ser Gln
145

<210> 292
<211> 146
<212> PRT

```
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
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<210> 206
<211> 248
<212> PRT
<213> Homo sapiens

<300>
<308> Genbank AAA85480
<309> 1996-01-19

<400> 206

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Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
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<211> 146

<213> Homo sapiens

<400> 292

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Gln Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 293
<211> 146
<212> PRT
<213> Homo sapiens

<400> 293

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Asn Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
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<212> PRT
<213> Homo sapiens

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
1 5 10 15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
20 25 30
Leu Gly Ile Leu Lys Asn Trp Gln Glu Glu Ser Asp Arg Lys Ile Met
35 40 45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
50 55 60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65 70 75 80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
85 90 95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
100 105 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
115 120 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
130 135 140
Ser Gln
145

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<212> PRT
<213> Homo sapiens

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
1 5 10 15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
20 25 30
Leu Gly Ile Leu Lys Asn Trp Asn Glu Glu Ser Asp Arg Lys Ile Met
35 40 45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
50 55 60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65 70 75 80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
85 90 95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
100 105 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
115 120 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
130 135 140
Ser Gln
145

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<211> 146
<212> PRT
<213> Homo sapiens

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
1 5 10 15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
20 25 30
Leu Gly Ile Leu Lys Asn Trp Lys Gln Glu Ser Asp Arg Lys Ile Met
35 40 45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
50 55 60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65 70 75 80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
85 90 95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
100 105 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
115 120 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
130 135 140
Ser Gln
145

<210> 297
<211> 146
<212> PRT
<213> Homo sapiens

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
1 5 10 15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
20 25 30
Leu Gly Ile Leu Lys Asn Trp Lys Asn Glu Ser Asp Arg Lys Ile Met
35 40 45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
50 55 60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65 70 75 80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
85 90 95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
100 105 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
115 120 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
130 135 140
Ser Gln
145

<210> 298
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<212> PRT
<213> Homo sapiens

<400> 298

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys His Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

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<212> PRT
<213> Homo sapiens

<400> 299

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Gln Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 300
<211> 146
<212> PRT
<213> Homo sapiens

<400> 300

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
```

```
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Asn Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 301
<211> 146
<212> PRT
<213> Homo sapiens

<400> 301

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Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu His Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 302
<211> 146
<212> PRT
<213> Homo sapiens

<400> 302

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
```

```
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Gln Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 303
<211> 146
<212> PRT
<213> Homo sapiens

<400> 303

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Asn Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 304
<211> 146
<212> PRT
<213> Homo sapiens

<400> 304

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
```

```
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Gln Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 305
<211> 146
<212> PRT
<213> Homo sapiens

<400> 305

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Asn Asn Phe Lys
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 306
<211> 146
<212> PRT
<213> Homo sapiens

<400> 306

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
```

```
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Gln
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 307
<211> 146
<212> PRT
<213> Homo sapiens

<400> 307

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Asn
    50                  55                  60
Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 308
<211> 146
<212> PRT
<213> Homo sapiens

<400> 308

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
```

```
         35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
     50                  55                  60
Gln Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                 85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
         115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
     130                 135                 140
Ser Gln
145
```

<210> 309
<211> 146
<212> PRT
<213> Homo sapiens

<400> 309

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
         35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
     50                  55                  60
Asn Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                 85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
         115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
     130                 135                 140
Ser Gln
145
```

<210> 310
<211> 146
<212> PRT
<213> Homo sapiens

<400> 310

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
         35                  40                  45
```

```
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Gln Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 311
<211> 146
<212> PRT
<213> Homo sapiens

<400> 311

```
Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys
 1               5                  10                  15
Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe
            20                  25                  30
Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met
        35                  40                  45
Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys
    50                  55                  60
Asp Asn Gln Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met
65                  70                  75                  80
Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu
                85                  90                  95
Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala
            100                 105                 110
Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys
        115                 120                 125
Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Gln Gly Arg Arg Ala
    130                 135                 140
Ser Gln
145
```

<210> 312
<211> 160
<212> PRT
<213> Homo sapiens

<400> 312

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Gln Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
```

```
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 313
<211> 160
<212> PRT
<213> Homo sapiens

<400> 313

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Asn Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 314
<211> 160
<212> PRT
<213> Homo sapiens

<400> 314

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Gln Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
```

65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 315
<211> 160
<212> PRT
<213> Homo sapiens

<400> 315
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Asn Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 316
<211> 160
<212> PRT
<213> Homo sapiens

<400> 316
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys His Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80

```
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                   85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
           100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
       115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
   130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 317
<211> 160
<212> PRT
<213> Homo sapiens

<400> 317

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Val Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                   85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
           100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
       115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
   130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 318
<211> 160
<212> PRT
<213> Homo sapiens

<400> 318

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Ile Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
```

```
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 319
<211> 160
<212> PRT
<213> Homo sapiens

<400> 319

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Val Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 320
<211> 160
<212> PRT
<213> Homo sapiens

<400> 320

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Ile Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
```

```
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 321
<211> 160
<212> PRT
<213> Homo sapiens

<400> 321

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Gln Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 322
<211> 160
<212> PRT
<213> Homo sapiens

<400> 322

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Asn Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
```

```
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 323
<211> 160
<212> PRT
<213> Homo sapiens

<400> 323

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu His Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 324
<211> 160
<212> PRT
<213> Homo sapiens

<400> 324

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Gln Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
```

```
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 325
<211> 160
<212> PRT
<213> Homo sapiens

<400> 325

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asn Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 326
<211> 160
<212> PRT
<213> Homo sapiens

<400> 326

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Ile Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
```

```
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 327
<211> 160
<212> PRT
<213> Homo sapiens

<400> 327

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Val Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 328
<211> 160
<212> PRT
<213> Homo sapiens

<400> 328

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Gln Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
```

Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 329
<211> 160
<212> PRT
<213> Homo sapiens

<400> 329
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Asn Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 330
<211> 160
<212> PRT
<213> Homo sapiens

<400> 330
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly His Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp

```
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160


<210> 331
<211> 160
<212> PRT
<213> Homo sapiens

<400> 331
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Ile Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160


<210> 332
<211> 160
<212> PRT
<213> Homo sapiens

<400> 332
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Val Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
```

Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 333
<211> 160
<212> PRT
<213> Homo sapiens

<400> 333
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Ile Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 334
<211> 160
<212> PRT
<213> Homo sapiens

<400> 334
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Gln Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn

145 150 155 160

<210> 335
<211> 160
<212> PRT
<213> Homo sapiens

<400> 335
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Asn Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 336
<211> 160
<212> PRT
<213> Homo sapiens

<400> 336
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser His Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 337
<211> 160
<212> PRT
<213> Homo sapiens

<400> 337

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Val Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 338
<211> 160
<212> PRT
<213> Homo sapiens

<400> 338

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Ile Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 339
<211> 160
<212> PRT
<213> Homo sapiens

<400> 339

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Ile Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 340
<211> 160
<212> PRT
<213> Homo sapiens

<400> 340

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Val Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 341
<211> 160
<212> PRT
<213> Homo sapiens

<400> 341

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe His Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 342
<211> 160
<212> PRT
<213> Homo sapiens

<400> 342

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Ile Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 343

<211> 160
<212> PRT
<213> Homo sapiens

<400> 343

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Gln Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 344
<211> 160
<212> PRT
<213> Homo sapiens

<400> 344

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Asn Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 345
<211> 160

<212> PRT
<213> Homo sapiens

<400> 345

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu His Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 346
<211> 160
<212> PRT
<213> Homo sapiens

<400> 346

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Gln Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 347
<211> 160

<212> PRT
<213> Homo sapiens

<400> 347

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Asn Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 348
<211> 160
<212> PRT
<213> Homo sapiens

<400> 348

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu His Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 349
<211> 160
<212> PRT

<213> Homo sapiens

<400> 349

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Ser Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 350
<211> 160
<212> PRT
<213> Homo sapiens

<400> 350

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Ala Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 351
<211> 160
<212> PRT
<213> Homo sapiens

<400> 351
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Gln Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 352
<211> 160
<212> PRT
<213> Homo sapiens

<400> 352
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Asn Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 353
<211> 160
<212> PRT
<213> Homo sapiens

<400> 353

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
His Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 354
<211> 160
<212> PRT
<213> Homo sapiens

<400> 354

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Gln Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 355
<211> 160
<212> PRT
<213> Homo sapiens

<400> 355

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asn Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 356
<211> 160
<212> PRT
<213> Homo sapiens

<400> 356

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Ser Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 357
<211> 160
<212> PRT
<213> Homo sapiens

<400> 357

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
```

```
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Ala Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 358
<211> 160
<212> PRT
<213> Homo sapiens

<400> 358

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Gln Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 359
<211> 160
<212> PRT
<213> Homo sapiens

<400> 359

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
```

```
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asn Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 360
<211> 160
<212> PRT
<213> Homo sapiens

<400> 360

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Gln Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 361
<211> 160
<212> PRT
<213> Homo sapiens

<400> 361

```
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
```

```
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Asn Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145                 150                 155                 160
```

<210> 401
<211> 209
<212> PRT
<213> Homo sapiens

<400> 401

```
Thr Gln Gln Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 402
<211> 209
<212> PRT
<213> Homo sapiens

<400> 402
Thr Gln Asn Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 403
<211> 209
<212> PRT
<213> Homo sapiens

<400> 403
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Gln Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160

Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 404
<211> 209
<212> PRT
<213> Homo sapiens

<400> 404
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asn Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 405
<211> 209
<212> PRT
<213> Homo sapiens

<400> 405
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Gln Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala

```
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 406
<211> 209
<212> PRT
<213> Homo sapiens

<400> 406

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1                  5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Asn Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 407
<211> 209
<212> PRT
<213> Homo sapiens

<400> 407

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu His Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 408
<211> 209
<212> PRT
<213> Homo sapiens

<400> 408

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Val Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
```

```
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 409
<211> 209
<212> PRT
<213> Homo sapiens

```
<400> 409
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Ile Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 410
<211> 209
<212> PRT
<213> Homo sapiens

```
<400> 410
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
```

```
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln His Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 411
<211> 209
<212> PRT
<213> Homo sapiens

<400> 411

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Gln Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
```

195 200 205
His

<210> 412
<211> 209
<212> PRT
<213> Homo sapiens

<400> 412
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Gln Arg Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 413
<211> 209
<212> PRT
<213> Homo sapiens

<400> 413
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Asn Arg Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu Arg Phe
85 90 95

```
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 414
<211> 209
<212> PRT
<213> Homo sapiens

<400> 414

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met His Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 415
<211> 209
<212> PRT
<213> Homo sapiens

<400> 415
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu His Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 416
<211> 209
<212> PRT
<213> Homo sapiens

<400> 416
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Gln Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala

```
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 417
<211> 209
<212> PRT
<213> Homo sapiens

<400> 417

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Gln Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 418
<211> 209
<212> PRT
<213> Homo sapiens

<400> 418

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Asn Thr Val Ala
    50                  55                  60
```

Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 419
<211> 209
<212> PRT
<213> Homo sapiens

<400> 419
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
50 55 60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65 70 75 80
Phe Val Thr Lys Cys Ala Phe Gln Ser Pro Pro Ser Cys Leu Arg Phe
85 90 95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
100 105 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
115 120 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
130 135 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145 150 155 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Ala Ala Ala
165 170 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
180 185 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
195 200 205
His

<210> 420

<211> 209
<212> PRT
<213> Homo sapiens

<400> 420

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Ala Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 421
<211> 209
<212> PRT
<213> Homo sapiens

<400> 421

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Ser Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
```

```
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 422
<211> 209
<212> PRT
<213> Homo sapiens

<400> 422

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Ala Pro Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 423
<211> 209
<212> PRT
<213> Homo sapiens

<400> 423

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
```

```
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 424
<211> 209
<212> PRT
<213> Homo sapiens

<400> 424

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1                5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ala Ser Cys Leu Arg Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
```

His

<210> 425
<211> 209
<212> PRT
<213> Homo sapiens

<400> 425

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu His Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
```

His

<210> 426
<211> 209
<212> PRT
<213> Homo sapiens

<400> 426

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Gln Phe
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
```

```
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 427
<211> 209
<212> PRT
<213> Homo sapiens

<400> 427

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Ile
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 428
<211> 209
<212> PRT
<213> Homo sapiens

<400> 428

```
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1               5                  10                  15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
            20                  25                  30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
        35                  40                  45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Val
                85                  90                  95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu
145                 150                 155                 160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Ala Ala Ala
                165                 170                 175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly
            180                 185                 190
Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Leu Val Glu
        195                 200                 205
His
```

<210> 499
<211> 248
<212> PRT
<213> Homo sapiens

<400> 499

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Val Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
```

```
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 500
<211> 248
<212> PRT
<213> Homo sapiens

<400> 500

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Ile Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 501
<211> 248
<212> PRT
<213> Homo sapiens

<400> 501

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Gln Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 502
<211> 248
<212> PRT
<213> Homo sapiens

<400> 502

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Asn Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
```

```
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 503
<211> 248
<212> PRT
<213> Homo sapiens

<400> 503

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1                5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Ser Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 504
<211> 248
<212> PRT
<213> Homo sapiens

<400> 504
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Ala Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 505
<211> 248
<212> PRT
<213> Homo sapiens

<400> 505
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Gln Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80

```
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                  85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
             100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
         115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
     130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                 165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
             180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
         195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
     210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                 245
```

<210> 506
<211> 248
<212> PRT
<213> Homo sapiens

<400> 506

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
             20                  25                  30
Val Pro Gly Met Asn Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
         35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
     50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                 85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
             100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
         115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
     130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                 165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
             180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
         195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
```

```
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 507
<211> 248
<212> PRT
<213> Homo sapiens

<400> 507

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Gln Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 508
<211> 248
<212> PRT
<213> Homo sapiens

<400> 508

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
```

```
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asn Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 509
<211> 248
<212> PRT
<213> Homo sapiens

<400> 509

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Gln Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
```

```
                 165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 510
<211> 248
<212> PRT
<213> Homo sapiens

<400> 510

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asn Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 511
<211> 248
<212> PRT
<213> Homo sapiens

<400> 511
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Gln Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 512
<211> 248
<212> PRT
<213> Homo sapiens

<400> 512
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asn Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp

```
         115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
     130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 513
<211> 248
<212> PRT
<213> Homo sapiens

<400> 513

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Gln Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 514
<211> 248
<212> PRT
<213> Homo sapiens

<400> 514
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Asn Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 515
<211> 248
<212> PRT
<213> Homo sapiens

<400> 515
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Ile Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val

65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 516
<211> 248
<212> PRT
<213> Homo sapiens

<400> 516
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Val Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205

Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 517
<211> 248
<212> PRT
<213> Homo sapiens

<400> 517
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Gln
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 518
<211> 248
<212> PRT
<213> Homo sapiens

<400> 518
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr

```
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Asn
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 519
<211> 248
<212> PRT
<213> Homo sapiens

<400> 519

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1                5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Val Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
```

```
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 520
<211> 248
<212> PRT
<213> Homo sapiens

<400> 520

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Ile Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 521
<211> 248
<212> PRT

<213> Homo sapiens

<400> 521

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Gln Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 522
<211> 248
<212> PRT
<213> Homo sapiens

<400> 522

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Asn Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
```

```
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 523
<211> 248
<212> PRT
<213> Homo sapiens

<400> 523

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Gln Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 524
<211> 248
<212> PRT
<213> Homo sapiens

<400> 524
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Asn Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 525
<211> 248
<212> PRT
<213> Homo sapiens

<400> 525
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val

65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Ile Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 526
<211> 248
<212> PRT
<213> Homo sapiens

<400> 526
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Val Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205

```
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 527
<211> 248
<212> PRT
<213> Homo sapiens

<400> 527

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Gln Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 528
<211> 248
<212> PRT
<213> Homo sapiens

<400> 528

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
```

```
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Asn Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 529
<211> 248
<212> PRT
<213> Homo sapiens

<400> 529

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1                  5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Gln Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
```

Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 530
<211> 248
<212> PRT
<213> Homo sapiens

<400> 530
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
1 5 10 15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
20 25 30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65 70 75 80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
85 90 95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Asn Pro Arg Leu Phe Thr Pro
100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
165 170 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
210 215 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225 230 235 240
Lys Glu Arg Glu Phe Gln Glu Val
245

<210> 531
<211> 248
<212> PRT

<213> Homo sapiens

<400> 531

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro His Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
                245
```

<210> 532
<211> 248
<212> PRT
<213> Homo sapiens

<400> 532

```
Glu Gly Ile Cys Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr
 1               5                  10                  15
Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Ser Arg Leu Phe Thr Pro
            100                 105                 110
```

```
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
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Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
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Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
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        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
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65                  70                  75                  80
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                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Ala Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
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Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
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Lys Glu Arg Glu Phe Gln Glu Val
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100 105 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
115 120 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
130 135 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145 150 155 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
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Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
180 185 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
195 200 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
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Lys Glu Arg Glu Phe Gln Glu Val
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35 40 45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
50 55 60

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Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Gln Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
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Lys Glu Arg Glu Phe Gln Glu Val
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Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Val Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
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Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
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        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
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<400> 537

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Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
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Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Ile Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
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 1               5                  10                  15
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            20                  25                  30
Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Gln Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
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Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
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Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
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225                 230                 235                 240
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        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Asn Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
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145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
Asn Ile Gln Ile Asn Glu Glu Asp Asn Glu Ile Ser Met Leu Gln Glu
225                 230                 235                 240
Lys Glu Arg Glu Phe Gln Glu Val
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Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser His Thr Ser Asp Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
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Lys Glu Arg Glu Phe Gln Glu Val
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Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Gln Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
        195                 200                 205
Ala Leu Tyr Trp Lys Lys Arg Gln Pro Ser Leu Thr Arg Ala Val Glu
    210                 215                 220
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Lys Glu Arg Glu Phe Gln Glu Val
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Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
        35                  40                  45
Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
    50                  55                  60
Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
65                  70                  75                  80
Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
                85                  90                  95
Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
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            100                 105                 110
Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
        115                 120                 125
Phe Val Val Ala Ser Glu Thr Ser Asn Cys Val Val Ser Ser Thr Leu
    130                 135                 140
Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
145                 150                 155                 160
Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
                165                 170                 175
Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His Trp Ala Ala
            180                 185                 190
Met Ala Leu Pro Ala Leu Phe Ser Leu Ile Ile Gly Phe Ala Phe Gly
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    210                 215                 220
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            20                  25                  30
Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45
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    50                  55                  60
Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65                  70                  75                  80
Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
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His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110
Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125
Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
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Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160
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PRELIMINARY AMENDMENT
DATED APRIL 8, 2004

04-12-04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: *Gantier, et al.*
Serial No.: 10/658,834
Filed: September 8, 2003
Conf.No.: 7681
Cust. No.: 20985
For: *RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY, THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES*
Art Unit: 1644
Examiner: Unassigned

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number
EV 399313518 US

Date of Deposit April 8, 2004
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 C.F.R. §1.10 on the date indicated above and addressed to:

MAIL STOP NON-FEE AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

04/8/2004
Date

Stephanie L. Seidman

TRANSMITTAL LETTER

MAIL STOP NON-FEE AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Transmitted herewith is a Preliminary Amendment (115 pages) for filing in connection with the above-identified application.

(X) The Commissioner is hereby authorized to charge any fees that may be due under 37 C.F.R. §§1.16-1.17 in connection with this paper or with this application during its entire pendency to Deposit Account No. 06-1050. A duplicate of this sheet is enclosed.

Respectfully submitted,

By:
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 37851-922 (17109-012001)

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Stephanie L. Seidman, Esq.
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-4777
Facsimile: (202) 626-7796
EMAIL: seidman@fr.com

04-12-04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Gantier *et al.*
Serial No.: 10/658,834
Conf. No.: 7681
Cust. No.: 20985
Filed: September 08, 2003

For: ***RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY, THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES***

Art Unit: 1644
Examiner: Not yet assigned

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number
EV 399313518 US
Date of Deposit April 8, 2004

I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 C.F.R. §1.10 on the date indicated above and addressed to:

MAIL STOP NON-FEE AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450, on this date.

4/8/04
Date

Stephanie L. Seidman

PRELIMINARY AMENDMENT

MAIL STOP NON-FEE AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Preliminary to examination of the above-captioned patent application, please amend the application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 20 of this paper.

Remarks begin on page 113 of this paper.

Amendments to the Specification:

Please replace the paragraph on page 1, lines 13-31, with the following amended paragraph:

This application is related to U.S. application Serial No. attorney dkt. no. 37851-922PC, entitled, "RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY, THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES," to Rene Gantier, Thierry Guyon, Manuel Vega and Lila Drittanti. This application also is related to U.S. application Serial No. ~~Attorney docket no. 37851-923,~~10/658,355 filed the same day herewith, entitled "RATIONAL DIRECTED PROTEIN EVOLUTION USING TWO-DIMENSIONAL RATIONAL MUTAGENESIS SCANNING," and to U.S. provisional application Serial No. 60/457,063, entitled "RATIONAL DIRECTED PROTEIN EVOLUTION USING TWO-DIMENSIONAL RATIONAL MUTAGENESIS SCANNING," filed March 21, 2003, and to U.S. provisional application Serial No. 60/410,258, entitled "RATIONAL DIRECTED PROTEIN EVOLUTION USING TWO-DIMENSIONAL RATIONAL MUTAGENESIS SCANNING," filed September 9, 2002, each to Rene Gantier, Thierry Guyon, Hugo Cruz Ramos, Manuel Vega and Lila Drittanti. This application also is related to co-pending U.S. application Serial No. 10/022,249, filed December 17, 2001, entitled "HIGH THROUGHPUT DIRECTED EVOLUTION BY RATIONAL MUTAGENESIS," to Manuel Vega and Lila Drittanti.

Please replace the paragraph on page 4, lines 2-17, with the following amended paragraph:

Provided herein are methods for directed evolution of families of proteins and resulting families of modified proteins. A family, such as the cytokine protein family, is initially identified. A property or phenotype for modification, such as resistance to proteolysis for increased stability in blood, is selected for modification. A representative member or members of the family, such as members of the ~~interfero~~ interferon α family, such as IFNα-2b or IFNα-2a, or interferon β family, is (are) selected. It is modified using any directed evolution

method and protein(s) with a desired phenotype are screened and identified. In addition, the 3-dimensional structure of the protein can be mapped to topologically and spatially identify the loci that are modified to achieve the phenotypic change. 3-dimensional structures of other members of the family are generated or obtained and compared with the modified family member. Loci in the other family members that correspond on the protein to those modified in the original protein are identified and modified. The resulting proteins can be tested to confirm that they exhibit the modified phenotype.

Please replace the paragraph on page 5, lines 7-19, with the following amended paragraph:

Also provided herein are modified (mutant) cytokine proteins, such as variants of IFNβ and IFNα, including IFNα-2b and IFNα-2a proteins and IFNβ proteins, that have altered, particularly, improved therapeutic properties, including higher stability compared to the unmodified forms. In particular, exemplary modified cytokines provided herein have increased stability, which, for example, improves their use as therapeutics. Among the modified cytokines provided herein are those that ~~exhibits~~ exhibit increased resistance to proteolysis compared to the unmodified cytokine. In particular, such resistance is at least 10%, 20%, 30%, 40%, 50%, 70%, 100% or more resistant to proteolysis compared to the unmodified cytokine. Also provided are cytokines that have increased anti-proliferative and/or antiviral activity and/or resistance to proteolysis compared to an unmodified cytokine.

Please replace the paragraph on page 16, line 23, to page 17, line 8, with the following amended paragraph:

As used herein, "is-HIT" refers to an *in silico* identified amino acid position along a target protein sequence that has been identified based on *i*) the particular protein properties to be evolved, *ii*) the protein's amino acid sequence, and/or *iii*) the known properties of the individual amino acids. These is-HIT loci

on the protein sequence are identified without use of experimental biological methods. For example, once the protein feature(s) to be optimized is (are) selected, diverse sources of information or previous knowledge (i.e., protein primary, secondary or tertiary structures, literature, patents) are exploited to determine those amino acid positions that may be amenable to improved protein fitness by replacement with a different amino acid. This step utilizes protein analysis "*in silico*." All possible candidate amino acid positions along a target ~~proteins~~ protein's primary sequence that might be involved in the feature being evolved are referred to herein as "*in silico* HITs" ("is-HITs"). The collection (library), of all is-HITs identified during this step represents the first dimension (target residue position) of the two-dimensional scanning methods provided herein.

Please replace the paragraph on page 21, line 17, to page 22, line 3, with the following amended paragraph:

As used herein, the phrase "unmodified target protein," "unmodified protein" or "unmodified cytokine," or grammatical variations thereof, refers to a starting protein that is selected for modification using the methods provided herein. The starting unmodified target protein can be the naturally occurring, wild type form of a protein. In addition, the starting unmodified target protein may have previously been altered or mutated, such that it differs from the native wild type isoform, but is nonetheless referred to herein as [[an]] a starting unmodified target protein relative to the subsequently modified proteins produced herein. Thus, existing proteins known in the art that have previously been modified to have a desired increase or decrease in a particular biological activity compared to an unmodified reference protein can be selected and used herein as the starting "unmodified target protein." For example, a protein that has been modified from its native form by one or more single amino acid changes and possesses either an increase or decrease in a desired activity, such as resistance to proteolysis, can be utilized with the methods provided herein as

the starting unmodified target protein for further modification of either the same or a different biological activity.

Please replace the paragraph on page 27, lines 10-13, with the following amended paragraph:

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the modified cytokines and compositions provided ~~herein~~ herein.

Please replace the paragraph on page 29, lines 15-25, with the following amended paragraph:

As used herein, nucleic acids include DNA, RNA and analogs thereof, including protein nucleic acids (PNA) and ~~mixture~~ mixtures thereof. Nucleic acids can be single or double stranded. When referring to probes or primers, optionally labeled, with a detectable label, such as a fluorescent or radiolabel, single-stranded molecules are contemplated. Such molecules are typically of a length such that they are statistically unique of low copy number (typically less than 5, generally less than 3) for probing or priming a library. Generally a probe or primer contains at least 14, 16 or 30 contiguous of sequence complementary to or identical a gene of interest. Probes and primers can be 10, 14, 16, 20, 30, 50, 100 or more nucleic acid bases long.

Please replace the paragraph on page 41, lines 15-29, with the following amended paragraph:

The 2-Dimensional rational scanning (or "2-dimensional scanning") methods for protein rational evolution provided herein (see, also copending U.S. application Serial No. ~~Attorney docket no. 923~~ 10/658,355, filed the same day herewith, based on U.S. provisional application Serial Nos. 60/457,063 and 60/410,258) are based on scanning over two dimensions. The first dimension

scanned is amino acid position along the protein sequence to identify is-HIT target positions, and the second dimension is the amino acid type selected for replacing a particular is-HIT amino acid position. An advantage of the 2-dimensional scanning methods provided herein is that at least one, and typically both, of the amino acid position scan and/or the replacing amino acid scan can be restricted such that fewer than all amino acids on the protein-backbone are selected for amino acid replacement; and/or fewer than all of the remaining 19 amino acids available to replace an original, such as native, amino acid are selected for replacement.

Please replace the paragraph on page 43, lines 12-30, with the following amended paragraph:

Provided herein is a method for directed evolution that includes identifying and selecting (using *in silico* analysis) specific amino acids and amino acid positions (referred to herein as is-HITs) along the protein sequence that are contemplated to be directly or indirectly involved in the feature being evolved. As noted, the 2-dimensional scanning methods provided include the following two-steps. The first step is an *in silico* search of a target protein's amino acid sequence to identify all possible amino acid positions that potentially can be targets for the activity being evolved. This is effected, for example, by assessing the effect of amino acid residues on the property(ies) to be altered on the protein, using any known standard software. The particulars of the *in silico* analysis is a function of the property to be modified. For example, in the example herein, a property that is altered <u>is</u> resistance of the protein to proteolysis.[[.]] To determine ~~aminoacid~~ <u>amino acid</u> residues that are potential targets as is-HITs, in this example, all possible target residues for proteases were first identified. The 3-dimensional structure of the protein was then considered in order to identify surface residues. Comparison of exposed residues with proteolytically cleavable residues yields residues that are targets for change.

Please replace the paragraph on page 64, lines 8-15, with the following amended paragraph:

Also provided are IFNα-2b proteins that contain a plurality of mutations based on the LEADs (see, *e.g.*, Tables 6 and 7, EXAMPLE 5, which ~~listscandidate~~ lists candidate LEADs and LEAD sites), are generated. These IFNα-2b proteins have activity that is further optimized. Examples of such proteins are described in the EXAMPLES. Other combinations of mutations can be prepared and tested as described herein to identify other LEADs of interest, particularly those that have further increased IFNα-2b antiviral activity or further increased resistance to proteolysis.

Please replace the paragraph on page 70, line 11 to page 71, line 22, with the following amended paragraph:

Provided herein are methods for designing and generating new versions of native or modified cytokines, such as IFNα-2b and IFNα-2a. Using these methods, the redesigned cytokine maintains either sufficient, typically equal or improved levels of a selected phenotype, such as a biological activity, of the original protein, while at the same time its amino acid sequence is changed by replacement of up to: at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 30%, at least 40% up to 50% or more of its native amino acids by the appropriate pseudo-wild type amino acids. Pseudo-wild type amino acids are those amino acids such that when they replace an original, such as native, amino acid at a given position on the protein sequence, the resulting protein displays substantially the same levels of biological activity (or sufficient activity for its therapeutic or other use) compared to the original, such as native, protein. In other embodiments, pseudo-wild type amino acids are those amino acids such that when they replace an original, such as native, amino acid at a given position on the protein sequence, the resulting protein displays the same

phenotype, such as levels of biological activity, compared to an original, typically a native, protein. Pseudo-wild type amino acids and the appropriate replacing positions can be detected and identified by any analytical or predictive means; such as for example, by performing an ~~Alanine scanning~~ alanine scan. Any other amino acid, particularly another amino acid that has a neutral effect on structure, such as Gly or Ser, also can be used for the scan. All those replacements of original, such as native, amino acids by Ala that do not lead to the generation of a HIT (a protein that has lost the desired biological activity), have either led to the generation of a LEAD (a protein with increased biological activity); or the replacement by Ala will be a neutral replacement, i.e., the resulting protein will display comparable levels of biological activity compared to the original, such as native, protein. The methods provided herein for protein redesign of cytokines, such as IFNα-2b and IFNα-2a, are intended to design and generate "artificial" (versus naturally existing) proteins, such that they consist of amino acid sequences not existing in [[Nature]] nature, but that display biological activities characteristic of the original, such as native, protein. These redesigned proteins are contemplated herein to be useful for avoiding potential side effects that might otherwise exist in other forms of cytokines in treatment of disease. Other uses of redesigned proteins provided herein are to establish cross-talk between pathways triggered by different proteins; to facilitate structural biology by generating mutants that can be crystallized while maintaining activity; and to destroy an activity of a protein without changing a second activity or multiple additional activities.

Please replace the paragraph on page 74, line 27, to page 75, line 6, with the following amended paragraph:

In addition, the IFNα-2b alanine scan revealed the following redesign-HITs having decreased antiviral activity at amino acid positions of IFNα-2b corresponding to SEQ ID NO:1, amino acid residues: 2, 7, 8, 11, 13, 15, 16, 23, 26, 28, 29, 30, 31, 32, 33, 53, 69, 91, 93, 98, and 101. Accordingly, in

particular embodiments where it is desired to decrease the [[viral]] antiviral activity of IFNα-2b or IFNα-2a, either one or more of insertions, deletions and/or replacements of the native amino acid residue(s) can be carried out at one or more of amino acid positions of IFNα-2b or IFNα-2a corresponding to SEQ ID NO:1, amino acid residues: 2, 7, 8, 11, 13, 15, 16, 23, 26, 28, 29, 30, 31, 32, 33, 53, 69, 91, 93, 98, and 101.

Please replace the paragraph on page 81, lines 20-31, with the following amended paragraph:

Also provided herein is a method of structural homology analysis for comparing proteins regardless of their underlying amino acid sequences. For a subset of proteins families, such as the family of human cytokines, this information is rationally exploited herein. Human cytokines all share a common helix bundle fold, which is used to structurally define the 4-helical cytokine superfamily in the structural classification of the protein database SCOP© (Structural Classification of Proteins; see, e.g., Murzin *et al.*, *J. Mol. Biol.*, 247:536-540, 1995 and ~~"http://scop.mrc-lmb.cam.ac.uk/scop/").~~ scop.mrc-lmb.cam.ac.uk/scop/). This superfamily includes three different families: 1) the interferons/interleukin-10 protein family (SEQ ID NOS: 1 and 182-200); 2) the long-chain cytokine family (SEQ ID NOS: 210-217); and 3) the short-chain cytokine family (SEQ ID NOS: 201-209).

Please replace the paragraph on page 86, lines 2-15, with the following amended paragraph:

Also provided herein are modified cytokines or cytokine structural homologues of IFNα-2b that are IFNα cytokines. These IFNα cytokines include, but are not limited to, IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8 and IFNα-consensus cytokine (see, SEQ ID No. 232). Accordingly, ~~amont the~~ among the modified IFNα cytokines provided herein are those with one or more amino acid replacements

at one or more target positions in either IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, or IFNα-consensus cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNα-2b modified proteins provided ~~herein~~herein. The replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-2a.

Please replace the paragraph on page 95, lines 4-9, with the following amended paragraph:

In [[ther]] other embodiments, the modified cytokines provided herein possess increased activity compared to the unmodified cytokine. Stability can be assessed by any *in vitro* or *in vivo* method, such as by measuring residual inhibition of viral replication or to stimulation of cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Please replace the paragraph on page 95, line 18, to page 96, line 2, with the following amended paragraph:

The 2D-scanning method and the 3D-scanning method (using structural homology) provided herein (see, copending U.S. application Serial No. 10/658,355, filed the same day herewith, based on U.S. provisional application Serial Nos. 60/457,063 and 60/410,258) were each applied to interferon β. Provided herein are mutant variants of the IFNβ protein that display improved stability as assessed by resistance to proteases (thereby possessing increased protein half-life) and at least comparable biological activity as assessed by antiviral or antiproliferation activity compared to the unmodified and wild type native IFNβ protein (SEQ ID NO: 196). The IFNβ mutant proteins provided herein confer a higher half-life and at least comparable biological activity with respect to the native sequence. Thus, the optimized IFNβ protein mutants

provided herein that possess increased resistance to proteolysis result in a decrease in the frequency of injections needed to maintain a sufficient drug level in serum, thus leading to, for example: *i*) higher comfort and acceptance by patients, *ii*) lower doses necessary to achieve comparable biological effects, and *iii*) as a consequence of (*ii*), likely attenuation of any secondary effects.

Please replace the paragraph on page 96, line 28, to page 96, line 17, with the following amended paragraph:

Two methodologies were used to address the improvements described above: (a) 2D-scanning methods were used to identify ~~aminoacid~~ amino acid changes that lead to improvement in protease resistance and to improvement in conformational stability, and (b) 3D-scanning, which employs structural homology methods ~~methods~~ also were used to identify ~~aminoaci~~ amino acid changes that lead to improvement in protease resistance. The 2D-scanning and 3D-scanning methods each were used to identify the amino acid changes on IFNβ that lead to an increase in stability when challenged either with proteases, human blood lysate or human serum. Increasing protein stability to proteases, human blood lysate or human serum is contemplated herein to provide a longer *in vivo* half-life for the particular protein molecules, and thus a reduction in the frequency of necessary injections into patients. The biological activities that have been measured for the IFNβ molecules are *i*) their capacity to inhibit virus replication when added to permissive cells previously infected with the appropriate virus, and *ii*) their capacity to stimulate cell proliferation when added to the appropriate cells. Prior to the measurement of biological activity, IFNβ molecules were challenged with proteases, human blood lysate or human serum during different incubation times. The biological activity measured, corresponds then to the residual biological activity following exposure to the proteolytic mixtures.

Please replace the paragraph on page 98, lines 5-17, with the following amended paragraph:

For the improvement of resistance to proteases, by 3D-scanning (structural homology):

1) Identifying some or all possible target sites (is-HITS) on the protein sequence that display an acceptable degree of structural homology around the ~~aminoacid~~ amino acid positions mutated in the LEAD molecules previously obtained for IFNα using 2D-scanning, and that are susceptible to digestion by one or more specific proteases; and

2) Identifying appropriate replacing amino acids, specific for each is-HIT, such that if used to replace one or more of the original amino acids at that specific is-HIT, they can be expected to increase the is-HIT's resistance to digestion by protease while at the same time, keeping the biological activity of the protein unchanged (these replacing amino acids are the candidate LEADs).

Please replace the paragraph on page 121, lines 7-15, with the following amended paragraph:

The optimized cytokine can be formulated for parenteral administration by injection e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form e.g., in ~~ampoules~~ ampules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder-lyophilized form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Please replace the paragraph on page 122, line 16, to page 123, line 17, with the following amended paragraph:

Methods of treatment of cytokine-mediated or cytokine-involved diseases and immunotherapeutic methods are provided. The modified cytokines can be used in any method of treatment for which the unmodified cytokine is used. Hence the modified cytokines can be used for treatment of all disorders noted herein for the respective cytokines and for those known to those of skill in the art for each of the others, such as immunotherapeutic treatment (interleukins) and red blood cell expansion and stem cell expansion. The following table summarizes exemplary uses in addition to those noted herein of exemplary modified cytokines provided herein:

Cytokine	**Exemplary Uses, Diseases and Treatment**
IL-10	anti-inflammatory treatment of chronic liver injury and disease; myeloma
Interferon-gamma	interstitial/idiopathic pulmonary fibrosis; adjunctive immunotherapy for immunosupressed patients
Granulocyte colony stimulating factor	Crohn's disease; cardiac disease; acquired and congenital neutropenias; asthma
Leukemia inhibitory factor	myocardial infarction; multiple sclerosis; prevention of axonal atrophy;olfactory epithelium replacement stimulation
Human growth hormone	growth hormone deficiency; acromegaly
Ciliary neurotrophic factor	retinal degeneration treatments; neurodegnerative diseases such as Huntingtons; auditory degenerative diseases
Leptin	obesity; pancreatitis; endometreosis
Oncostatin M	chronic infammatory diseases; rheumatoid arthritis; multiple sclerosis; tissue damage supression
Interleukin-6	protection from liver injury; Crohn's disease; hematopoietic associated diseases
Interleukin-12	coksakievirus treatment;neuroblastoma; melanoma, renal cell carcinoma; mucosal immunity induction
Erythropoietin	hypoxia; myocardial ischemia; anemia with renal failure and cancer treatments
Granulocyte-macrophage colony stimulating factor	stimulate antigen presenting cells; anti-tumor activity for leukemia, melanoma, and breast, liver and renal cell carcinomas; adjunctive immunotherapy for immunosupressed patients; automimmune disease

Cytokine	Exemplary Uses, Diseases and Treatment
Interleukin-2	immune reactivation after chemotherapy; melanoma; colon carcinoma
Interleukin-3	leukemia cell targeting; motor neuropathy; amyotrophic lateral sclerosis; asthma
Interleukin-4	allergic asthma; lupus
Interleukin-5	treatment for parasites;asthma; allergic diseases accompanied by eosinophilia
Interleukin-13	intracellular infections; B-cell cancers; asthma
Flt3 ligand	[[prostatate]] prostate cancer; myeloid leukemia; engraftment of allogenic hematopietic stem cells
Stem cell factor	hepatic injury; asthma; hematopoietic engraftment

Please replace the paragraph on page 127, line 22, to page 128, line 10, with the following amended paragraph:

Lead mutants of Interferon alpha were first generated in the pSSV9-IFNa-EcoRI plasmid. With the only exception of E159H and E159Q, all mutants were amplified using the primers below. Primers contained NdeI (in Forward) and BamHI (in Reverse) restriction sites:

FOR-IFNA-5' AACATATGTGTGATCTGCCTCAAACCCACAGCCTGGGTAGC 3' (SEQ ID No. 1306; and

REV-IFNA-5' AAGGATCCTCATTCCTTACTTCTTAAACTTTCTTGCAAGTTTGTTG 3' (SEQ ID No. 1305)

Mutants E159H and E159Q were amplified using the following primers on reverse side (primer forward was the same than described above):

REV-IFNA-E159H-5' AAGGATCCTCATTCCTTACTTCTTAAACTGTGTTGCAAGTTTGTTG 3' SEQ ID No. 1304 above; and

REV-IFNA-E159Q-5' AAGGATCCTCATTCCTTACTTCTTAAACTCTGTTGCAAGTTTGTTG 3' SEQ ID No. 1305.

Mutants were amplified with Pfu Turbo Polymerase (Stratagene) ~~according~~. PCR products were cloned into pTOPO plasmid (Zero Blunt TOPO PCR cloning kit,

Invitrogen). The presence of the desired mutations was checked by automatic sequencing. The NdeI + BamHI fragment of the pTOPO-IFNa positive clones was then cloned into NdeI + BamHI sites of the pET11 plasmid.

Please replace the paragraph on page 130, lines 5-16, with the following amended paragraph:

IFNα-2b mutants were produced in 293 human embryo kidney (HEK) cells (obtained from ATCC), using Dubelcco's modified Eagle's medium supplemented with glucose (4.5 g/L; Gibco-BRL) and fetal bovine serum (10%, Hyclone). Cells were transiently transfected with the plasmids encoding the IFNα-2b mutants as follows: 0.6 x 10^5 cells were seeded into 6 well-plates and grown for 36 h before ~~transfection~~transfection. Confluent cells at about [[70%,]]70% were supplemented with 2.5 μg of plasmid (IFNα-2b mutants) and 10 mM poly-ethylene-imine (25 KDa PEI, Sigma-Aldrich). After gently shaking, cells were incubated for 16 h. Then, the culture medium was changed with 1 ml of fresh medium supplemented with 1% of serum. IFNα-2b was measured on culture supernatants obtained 40 h after transfection and stored in aliquots at -80 °C until use.

Please replace the paragraph on page 131, line 28, to page 132, line 3, with the following amended paragraph:

Samples contained 1 mg of protein at 0.3 mg/ml (5 ml in total) in buffer. The GdnHCl ~~(Hydrochloride Guanidium)~~ (Guanidinium hydrochloride) present in the samples was eliminated by dialysis (minimum membrane cut = 10 kDa) overnight at 4°C against buffer ~~(1litre)~~(1 litre) (final concentration of GdnHCl : 43 [[Mm]] mM). Next, samples were further dialysed against ~~1litre~~ 1 litre of buffer during [[2:30h.]]2.5 hours. This step was repeated two additional times. After dialysis, very little precipitate was visible.

Please replace the paragraph on page 134, lines 1-13, with the following amended paragraph:

After 24 hours of growth, a 1/1000 EMC virus dilution solution was placed in each well except for the cell control row. Plates were returned to the CO_2 incubator for 48 hours. Then, the medium was aspirated and the cells were stained for 1 hour with 100 µl of Blue staining ~~solutio~~ solution to determine the proportion of intact cells. Plates were washed in a distilled water bath. The cell bound dye was extracted using 100 µl of ethylene-glycol mono-ethyl-ether (Sigma). The absorbance of the dye was measured using an Elisa plate reader (Spectramax). The antiviral activity of IFN α-2b samples (expressed as number of IU/mg of proteins) was determined as the concentration needed for 50% protection of the cells against EMC virus-induced cytopathic effects. For proteolysis experiments, each point of for the kinetic measurements was assessed at 500 and 166 pg/ml in triplicate.

Please replace the paragraph on page 135, line 27, to page 136, line 7, with the following amended paragraph:

The percent of residual IFN α-2b activity over time of exposure to proteases was evaluated by a kinetic study using either (a) 15 pg of chymotrypsin (10%wt/wt), (b) a lysate of human blood at dilution 1/100, (c) 1.5 pg of protease mixture, or (d) human serum. Incubation times were: 0 h, 0.5 h, 1 h, 4 h, 8 h, 16 h, 24 h and 48 h. Briefly, 20 µl of each proteolytic sample (proteases, serum, ~~bnlood~~ blood) was added to 100 µl of IFN α-2b at 1500 pg/ml (500U/ml) and incubated for variable times, as indicated. At the appropriate time points, 10 µl of anti-proteases mixture, mini EDTA free, Roche (one tablet was dissolved in 10 ml of DMEM and then diluted to 1/500) was added to each well in order to stop proteolysis reactions. Biological activity assays were then performed as described for each sample in order to determine the residual activity at each time point.

Please replace the paragraph on page 136, lines 19-31, with the following amended paragraph:

IFNα –2b mutants selected on the basis of their overall performance in vitro, were tested for pharmacokinetics in mice in order to have an indication of their half-life in blood in vivo. Mice were treated by subcutaneous (SC) injection with ~~aliquots~~ aliquots of each of a number of selected lead mutants. Blood was collected at increasing time points between 0.5 and 48 [[hs]]hours after injection. Inmediatedly after collection, 20 ml of anti-protease solution were added to each blood sample. Serum was obtained for further ~~analysis.Residual~~analysis. Residual IFN-α activity in blood was determined using the tests described in the precedent sections for in vitro characterization. Wild-type [[IFN α]]IFN-α (that had been produced in bacteria under comparable conditions as the lead mutants) as well as a pegylated derivative of IFN α, Pegasys (Roche), also were tested for pharmacokinetics in the same experiments.

Please replace the paragraph on page 140, line 30, to page 141, line 5, with the following amended paragraph:

The creation of N-glycosylation sites on the protein was a second strategy that was used to stabilize [[IFNα-2b]]IFNα-2b. Natural human IFNα-2b contains a unique *O*-glycosylation site at position 129 (the numbering corresponds to the mature protein; SEQ ID NO:1), however, no *N*-glycosylation sites are found in this sequence. N-glycosylation sites are defined by the N-X-S or N-X-T consensus sequences. Glycosylation has been found to play a role in protein stability. For example, glycosylation has been found to increase bioavailability via higher metabolic stability and reduced clearance. In order to generate more stable IFNα-2b variants, the N-glycosylation consensus sequences indicated above were introduced in the IFNα-2b sequence by mutagenesis. Variants of IFNα-2b carrying new glycosylation sites were assessed as previously described.

Please replace the paragraph on page 149, 28, to page 150, line 2 with the following amended paragraph:

The pSSV9 CMV 0.3 pA was cut by *Pvu*II and religated (this step gets rid of the ITR functions), prior to the introduction of a new *Eco*RI restriction site by Quickchange mutagenesis (Stratagene). The ~~oligonucleotides~~ oligonucleotide sequences used, follow:

EcoRI forward primer: 5'-GCCTGTATGATTTATTGGATGTTGGAATTCCCTGATGCGGTATTTTCTCCTTACG-3' (SEQ ID NO: 218)

EcoRI reverse prime: 5'-CGTAAGGAGAAAATACCGCATCAGGGAATTCCAACATCCAATAAATCATACAGGC-3' (SEQ ID NO: 219)

Please replace the paragraph on page 151, lines 12-21, with the following amended paragraph:

Two activities were measured directly on IFN samples: antiviral and antiproliferation activities. Dose (concentration) - response (activity) experiments for antiviral or antiproliferation activity allowed for the calculation of the 'potency' for antiviral and antiproliferation activities, respectively. Antiviral and antiproliferation activities also were measured after incubation with proteolytic samples such as specific proteases, mixtures of selected proteases, human serum or human blood. Assessment of activity following incubation with proteolytic samples allowed to determine the residual (antiviral or antiproliferation) activity [[an.d]] and the respective kinetics of half-life upon exposure to ~~proteases~~ proteases.

Please replace the paragraph on page 151, lines 23-29, with the following amended paragraph:

Antiviral activity of IFN β was determined by the capacity of the cytokine to protect Hela cells against EMC (mouse encephalomyocarditis) virus-induced

cytopathic effects. The day before, Hela cells ($2x10^5$ cells/ml) were seeded in flat-bottomed 96-well plates containing 100 μl/well of Dulbecco's MEM-Glutamaxl-sodium pyruvate medium supplemented with 5% SVF and 0.2% of gentamicin. Cells were growth at 37°C in an atmosphere of 5% CO_2 for 24 [[hours]]hours.

Please replace the paragraph on page 154, lines 1-11, with the following amended paragraph:

The percent of residual IFN β activity over time of exposure to proteases was evaluated by a kinetic study using 1.5 pg of protease mixture. Incubation times were: 0 h, 0.5 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h. Briefly, 20 μl of each proteolytic sample (proteases, serum, ~~bnlood~~ blood) was added to 100 μl of IFN β at 400 and 800 pg/ml and incubated for variable times, as indicated. At the appropriate time points, 10 μl of anti-proteases mixture, mini EDTA free, Roche (one tablet was dissolved in 10 ml of DMEM and then diluted to 1/500) was added to each well in order to stop proteolysis reactions. Biological activity assays were then performed as described for each sample in order to determine the residual activity at each time point.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (Currently amended): A modified cytokine that exhibits increased resistance to proteolysis compared to the unmodified cytokine or a modified cytokine selected from the group consisting of modified cytokines comprising a sequence of amino acids set forth in any of SEQ ID [[Nos.]]NOS: 2-181, 233-1303 or a structural homolog thereof.

Claim 2 (Currently amended): The modified cytokine of claim 1, selected from the group consisting of a member of the interferons/interleukin-10 protein family, a member of the long-chain cytokine family and a member of the short-chain cytokine family, wherein the modified cytokine is a modified interferon α of any of SEQ ID [[Nos.]]NOS: 87, 89, 90, 93, 96, 101, 103, 107, 124, 979, 980, 983, 984, 985, 986 and 987 or a cytokine modified on the basis of 3-dimensional structural homology with any of SEQ ID [[Nos.]]NOS: 87, 89, 90, 93, 96, 101, 103, 107, 124, 979, 980, 983, 984, 985, 986 and 987.

Claim 3 (Original): The modified cytokine of claim 1 selected from the group consisting of interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha-2a (IFNα-2a), interferon alpha-2b (IFNα-2b), and interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

Claim 4 (Original): The modified cytokine of claim 1, that is an interferon.

Claim 5 (Currently amended): The modified cytokine of claim 1, that is an interferon α-2b (IFNα-2b), interferon α-2a (IFNα-2a), interferon α-2c (IFNα-2c) or an interferon having the sequence set forth in SEQ ID [[No.]]NO: 232.

Claim 6 (Currently amended): A modified cytokine of claim 4, that is IFNα-2b or IFNα-2a or IFNα-2C selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID [[No.]]NOS: 1 or 182, corresponding to the replacement of: L by V at position 3; L by I at position 3; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at

position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165,

wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

Claim 7 (Original): The modified cytokine of claim 6, wherein:

the protein is human;

has more resistance to proteolysis than the unmodified protein; and

the protein is selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID NOS:1 or 182, corresponding to: F by V at position 27; R by H at position 33; E by Q at position 41; E by H at position 41; E by Q at position 58; E by H at position 58; E by Q at position 78; E by H at position 78; Y by H at position 89; E by Q at position 107; E by H at position 107; P by A at position 109; L by V at position 110; M by V at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; K by Q at position 133; K by T at position 133; E by Q at position 159 and E by H at position 159.

Claim 8 (Original): A modified IFNα-2b or IFNα-2a cytokine of claim 5 selected from the group consisting of proteins comprising one or more sets of dual-amino acid replacements in SEQ ID NOS:1 or 182, corresponding to:

D by N at position 2 and P by S at position 4;

D by N at position 2 and P by T at position 4;

L by N at position 3 and Q by S at position 5;

L by N at position 3 and Q by T at position 5;

P by N at position 4 and T by S at position 6;

P by N at position 4 and T by T at position 6;

Q by N at position 5 and H by S at position 7;

Q by N at position 5 and H by T at position 7;

T by N at position 6 and S by S at position 8;

T by N at position 6 and S by T at position 8;

H by N at position 7 and L by S at position 9;

H by N at position 7 and L by T at position 9;

S by N at position 8 and G by S at position 10;

S by N at position 8 and G by T at position 10;

L by N at position 9 and S by S at position 11;

L by N at position 9 and S by T at position 11;

M by N at position 21 and K by S at position 23;

M by N at position 21 and K by T at position 23;

R by N at position 22 and I by S at position 24;

R by N at position 22 and I by T at position 24;

R or K by N at position 23 and S by S at position 25;

R or K by N at position 23 and S by T at position 25;

I by N at position 24 and L by S at position 26;

I by N at position 24 and L by T at position 26;

S by N at position 25 and F by S at position 27;

S by N at position 25 and F by T at position 27;

L by N at position 26 and S by S at position 28;

L by N at position 26 and S by T at position 28;

S by N at position 28 and L by S at position 30;

S by N at position 28 and L by T at position 30;

L by N at position 30 and D by S at position 32;

L by N at position 30 and D by T at position 32;

K by N at position 31 and R by S at position 33;

K by N at position 31 and R by T at position 33;

D by N at position 32 and H by S at position 34;

D by N at position 32 and H by T at position 34;

R by N at position 33 and D by S at position 35;

R by N at position 33 and D by T at position 35;

H by N at position 34 and F by S at position 36;

H by N at position 34 and F by T at position 36;

D by N at position 35 and G by S at position 37;

D by N at position 35 and G by T at position 37;

F by N at position 36 and F by S at position 38;

F by N at position 36 and F by T at position 38;

G by N at position 37 and P by S at position 39;

G by N at position 37 and P by T at position 39;

F by N at position 38 and Q by S at position 40;

F by N at position 38 and Q by T at position 40;

P by N at position 39 and E by S at position 41;

P by N at position 39 and E by T at position 41;

Q by N at position 40 and E by S at position 42;

Q by N at position 40 and E by T at position 42;

E by N at position 41 and F by S at position 43;

E by N at position 41 and F by T at position 43;

E by N at position 42 and G by S at position 44;

E by N at position 42 and G by T at position 44;

F by N at position 43 and N by S at position 45;

F by N at position 43 and N by T at position 45;

G by N at position 44 and Q by S at position 46;

G by N at position 44 and Q by T at position 46;

N by N at position 45 and F by S at position 47;

N by N at position 45 and F by T at position 47;

Q by N at position 46 and Q by S at position 48;

Q by N at position 46 and Q by T at position 48;

F by N at position 47 and K by S at position 49;

F by N at position 47 and K by T at position 49;

Q by N at position 48 and A by S at position 50;

Q by N at position 48 and A by T at position 50;
K by N at position 49 and E by S at position 51;
K by N at position 49 and E by T at position 51;
A by N at position 50 and T by S at position 52;
A by N at position 50 and T by T at position 52;
S by N at position 68 and K by S at position 70;
S by N at position 68 and K by T at position 70;
K by N at position 70 and S by S at position 72;
K by N at position 70 and S by T at position 72;
A by N at position 75 and D by S at position 77;
A by N at position 75 and D by T at position 77;
D by N at position 77 and T by S at position 79;
D by N at position 77 and T by T at position 79;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
Q by N at position 101 and V by S at position 103;
Q by N at position 101 and V by T at position 103;
G by N at position 102 and G by S at position 104;
G by N at position 102 and G by T at position 104;
V by N at position 103 and V by S at position 105;
V by N at position 103 and V by T at position 105;
G by N at position 104 and T by S at position 106;
G by N at position 104 and T by T at position 106;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;
E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;
T by N at position 108 and I by S at position 110;

T by N at position 108 and I by T at position 110;
K by N at position 134 and S by S at position 136;
K by N at position 134 and S by T at position 136;
S by N at position 154 and N by S at position 156;
S by N at position 154 and N by T at position 156;
T by N at position 155 and L by S at position 157;
T by N at position 155 and L by T at position 157;
N by N at position 156 and Q by S at position 158;
N by N at position 156 and Q by T at position 158;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
Q by N at position 158 and S by S at position 160;
Q by N at position 158 and S by T at position 160;
E by N at position 159 and L by S at position 161;
E by N at position 159 and L by T at position 161;
S by N at position 160 and R by S at position 162;
S by N at position 160 and R by T at position 162;
L by N at position 161 and S by S at position 163;
L by N at position 161 and S by T at position 163;
R by N at position 162 and K by S at position 164;
R by N at position 162 and K by T at position 164;
S by N at position 163 and E by S at position 165; and
S by N at position 163 and E by T at position 165,

wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

Claim 9 (Original): A modified IFNα-2b or IFNα-2a mutant cytokine of claim 5 selected from the group consisting of proteins comprising one or more sets of dual amino acid replacements in SEQ ID NOS:1 or 182, corresponding to:

Q by N at position 5 and H by S at position 7;

P by N at position 39 and E by S at position 41;
P by N at position 39 and E by T at position 41;
Q by N at position 40 and E by S at position 42;
Q by N at position 40 and E by T at position 42;
E by N at position 41 and F by S at position 43;
E by N at position 41 and F by T at position 43;
F by N at position 43 and N by S at position 45;
G by N at position 44 and Q by T at position 46;
N by N at position 45 and F by S at position 47;
N by N at position 45 and F by T at position 47;
Q by N at position 46 and Q by S at position 48;
F by N at position 47 and K by S at position 49;
F by N at position 47 and K by T at position 49;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;
E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
E by N at position 159 and L by S at position 161; and
E by N at position 159 and L by T at position 161.

Claim 10 (Original): A modified cytokine of claim 5, further comprising one or more pseudo-wild type mutations.

Claim 11 (Original): The modified cytokine of claim 10 that is IFNα-2b or IFNα-2a.

Claim 12 (Original): A modified IFNα-2b or IFNα-2a cytokine of claim 11, comprising one or more pseudo-wild type mutations at amino acid positions of IFNα-2b or IFNα-2a corresponding to SEQ ID NOS:1 or 182, amino acid residues: 9, 10, 17, 20, 24, 25, 35, 37, 41, 52, 54, 56, 57, 58, 60, 63, 64, 65, 76, 89, and 90, wherein the mutations are selected from the group consisting of one or more of insertions, deletions and replacements of the native amino acid residue(s), wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a protein set forth in SEQ ID NOS:1 or 182.

Claim 13 (Currently amended): A modified IFNα-2b or IFNα-2a cytokine of claim 11, comprising one wherein the pseudo-wild type replacements are one or more mutations in SEQ ID [[No.]]NOS: 1 or 182 corresponding to:

P by A at position 4; Q by A at position 5,
T by A at position 6; L by A at position 9,
LG by A at position 10; L by A at position 17,
Q by A at position 20; I by A at position 24,
S by A at position 25; D by A at position 35,
G by A at position 37; G by A at position 39;
E by A at position 41; E by A at position 42
E by A at position 51; T by A at position 52,
P by A at position 54; V by A at position 55
L by A at position 56; H by A at position 57,
E by A at position 58; I by A at position 60,
I by A at position 63; F by A at position 64,
N by A at position 65; W by A at position 76,
D by A at position 77; E by A at position 78
L by A at position 81; Y by A at position 85

Y by A at position 89; Q by A at position 90
G by A at position 104; L by A at position 110
S by A at position 115 and E by A at position 146.

Claim 14 (Currently amended): A modified cytokine of claim 5, comprising one or more pseudo-wild type mutations at amino acid positions of IFNα-2b, IFNα-2c or a protein having the sequence set forth in SEQ ID [[No.]]NO: 232 corresponding amino acid residues: 4, 5, 6, 9, 10, 17, 20, 24, 25, 35, 37, 39, 41, 42, 51, 52, 54, 56, 57, 58, 60, 63, 64, 65, 76, 77, 78, 81, 85, 89, 90, 104, 110, 115 and 146 to SEQ ID No. 1, 182 or 232, wherein the mutations are selected from the group consisting of one or more of insertions, deletions and replacements of the native amino acid residue(s), wherein residue 1 corresponds to residue 1 of the mature interferon set forth in SEQ ID [[No.]]NOS:1, 182 or 232.

Claim 15 (Currently amended): The modified ~~cytokin~~ cytokine of claim 14, wherein the ~~pseudowild-type~~ pseudo-wild type replacements are one or more mutations selected from:

P by A at position 4; Q by A at position 5;
T by A at position 6; L by A at position 9;
LG by A at position 10; L by A at position 17;
Q by A at position 20; I by A at position 24;
S by A at position 25; D by A at position 35;
G by A at position 37; G by A at position 39;
E by A at position 41; E by A at position 42;
E by A at position 51; T by A at position 52;
P by A at position 54; V by A at position 55;
L by A at position 56; H by A at position 57;
E by A at position 58; I by A at position 60;
I by A at position 63; F by A at position 64;

N by A at position 65; W by A at position 76;

D by A at position 77; E by A at position 78;

L by A at position 81; Y by A at position 85;

Y by A at position 89, Q by A at position 90;

G by A at position 104; L by A at position 110;

S by A at position 115 and E by A at position 146, wherein the positions correspond to SEQ ID [[No.]]NOS: 1, 182, 185 or 232.

Claim 16 (Original): A modified cytokine of claim 5 that has increased antiviral activity compared to the unmodified cytokine.

Claim 17 (Original): The modified cytokine of claim 16, wherein antiviral activity is assessed by measuring replication by reverse transcription quantification PCR (RT-qPCR).

Claim 18 (Original): A modified cytokine of claim 5 that has more antiviral activity than antiproliferative activity compared to the unmodified cytokine.

Claim 19 (Original): The modified cytokine of claim 18, wherein antiproliferative activity is assessed by measuring cell proliferation in the presence of the cytokine.

Claim 20 (Currently amended): A modified cytokine of claim 5 that [[that]] binds to an IFN receptor, but exhibits decreased antiviral activity and decreased antiproliferative activity relative to its receptor binding activity when compared to the unmodified cytokine.

Claim 21 (Original): A modified cytokine of claim 1, comprising two or more mutations.

Claim 22 (Original): The modified cytokine of claim 21 that is a modified IFNα-2b cytokine.

Claim 23 (Currently amended): A modified cytokine of claim 1, wherein the cytokine comprises the sequence of amino acids set forth in any of SEQ ID [[Nos]]NOS: 2 through 181, wherein the arginine at position 23 is replaced with a lysine.

Claim 24 (Original): A modified cytokine of any claim 1 selected from the group consisting of interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha (IFNα), interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

Claim 25 (Original): A collection of the modified cytokines of claim 1, wherein the modified cytokines contain one or a plurality of mutations.

Claim 26 (Original): A nucleic acid molecule encoding a modified cytokine of claim 1.

Claim 27 (Original): A vector comprising a nucleic acid molecule of claim 26.

Claim 28 (Original): A eukaryotic cell, comprising the vector of claim 27.

Claim 29 (Original): A collection of nucleic acid molecules comprising a plurality of the molecules of claim 26.

Claim 30 (Original): A collection of nucleic acid molecules comprising a plurality of the vectors of claim 27.

Claim 31 (Currently amended): A method for expression of a modified cytokine, comprising:

introducing a nucleic acid of claim 26 into a host; and

culturing the [[cell]] host, under conditions and in which the modified encoded cytokines are expressed.

Claim 32 (Original): The method of claim 31, wherein the nucleic acid is introduced into a host cell.

Claim 33 (Currently amended): The method of claim 31, wherein the cytokine is a modified IFNα-2b, ~~IFNα-2a cytokine~~ IFNα-2a, IFNα-2c or interferon of SEQ ID [[No.]]NO: 232.

Claim 34 (Original): The method of claim 31, wherein the host is a eukaryotic host cell.

Claim 35 (Currently Amended): The method of claim [[34,]]31, wherein the modified cytokine is glycosylated.

Claim 36 (Original): The method of claim 31, wherein expression is effected *in vivo*.

Claim 37 (Original): The method of claim 31, wherein expression is effected *in vitro*.

Claim 38 (Original): The method of claim 31, wherein expression is effected in a cell-free system.

Claim 39 (Currently amended): A modified cytokine <u>of</u> claim 2, comprising two or more mutations.

Claim 40 (Original): A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

Claim 41 (currently amended): A modified cytokine of claim 5 that exhibits greater resistance to proteolysis compared to the unmodified cytokine, comprising one or more amino acid replacements at one or more positions on the cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFN*α*-2b or IFN*α*-2a or IFN*α*-2c or consensus IFN*α* of SEQ ID [[No.]]<u>NO:</u> 232.

Claim 42 (Currently amended): A modified cytokine of claim 41, wherein the resistance to proteolysis is measured by mixing it with a protease ~~in vitro~~<u>*in vitro*</u>, incubation with blood or incubation with serum.

Claim 43 (Currently amended): A modified cytokine of claim 1 that is a structural homolog of IFN*α*-2b, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of the modified IFN*α*-2b or IFN*α*-2a or [[IFN*α* 2c]]<u>IFN*α*-2c</u> or an interferon of SEQ ID [[No.]]<u>NO:</u> 232.

Claim 44 (Original): A modified cytokine of claim 43, wherein the homolog has increased resistance to proteolysis compared to its unmodified cytokine counterpart, wherein the resistance to proteolysis is measured by mixture with a protease *in vitro*, incubation with blood or incubation with serum.

Claim 45 (Original): The cytokine of claim 44 that is an IFN*α* cytokine.

Claim 46 (Original): The cytokine of claim 45, selected from the group consisting of IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, and IFNα-consensus cytokine.

Claim 47 (Currently amended): A modified cytokine of claim 1 that is modified IFNα-2a cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID [[NO.]]NO: 182 in the IFNα-2a corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of unmodified IFNα-2b, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-2a.

Claim 48 (Orignal): The modified IFNα-2a of claim 47, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 182, corresponding to amino acid positions 41, 58, 78, 107, 117, 125, 133 and 159.

Claim 49 (Currently amended): A modified IFNα-c cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID [[NO.]]NO: 183 in the IFNα-c corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-c.

Claim 50 (Original): The modified IFNα-c of claim 49, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 183, corresponding to amino acid positions 41, 59, 79, 108, 118, 126, 134 and 160.

Claim 51 (Currently amended): A modified IFNα-c, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 185 in the IFNα-2c corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-2c.

Claim 52 (Original): The modified IFNα-2c cytokine of claim 51, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 185, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

Claim 53 (Currently amended): A modified IFNα-d cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 186 in the IFNα-d corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-d.

Claim 54 (Original): The IFNα-d modified cytokine of claim 53, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 186, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

Claim 55 (Currently amended): A modified IFNα-5 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO:

187 in the IFNα-5 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-5.

Claim 56 (Original): The IFNα-5 modified cytokine of claim 55, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 187, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 57 (Currently amended): A modified IFNα-6 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 188 in the IFNα-6 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-6.

Claim 58 (Original): The IFNα-6 modified cytokine of claim 57, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 188, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

Claim 59 (Currently amended): A modified IFNα-4 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 189 in the IFNα-4 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of

claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-4.

Claim 60 (Original): The IFNα-4 modified cytokine of claim 59, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 189, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

Claim 61 (Currently amended): A modified IFNα-4b cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 190 in the IFNα-4b corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-4b.

Claim 62 (Original): The IFNα-4b modified cytokine of claim 61, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 190, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

Claim 63 (Currently amended): A modified IFNα-I cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 191 in the IFNα-I corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as

assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-I.

Claim 64 (Original): The IFNα-I modified cytokine of claim 63, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 191, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 65 (Currently amended): A modified IFNα-J cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 192 in the IFNα-J corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-J.

Claim 66 (Original): The IFNα-J modified cytokine of claim 65, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 192, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 67 (Currently amended): A modified IFNα-H cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 193 in the IFNα-H corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-H.

Claim 68 (Original): The IFNα-H modified cytokine of claim 67, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 193, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 69 (Currently amended): An IFNα-F cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 194 in the IFNα-F corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-F.

Claim 70 (Original): The IFNα-F modified cytokine of claim 69, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 194, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 71 (Currently amended): An IFNα-8 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 195 in the IFNα-8 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-8.

Claim 72 (Original): The IFNα-8 modified cytokine of claim 71, that is human and is selected from the group consisting of cytokines comprising one or more

single amino acid replacements in SEQ ID NO: 195, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 73 (Currently amended): An IFNα-consensus cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 232 in the IFNα-consensus cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNα-consensus.

Claim 74 (Original): The modified cytokine of claim 1 that is an IFNα-consensus cytokine, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 232, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

Claim 75 (Currently amended): A modified IFNβ cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 196 in the [[IFNα-β]]IFNβ cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNβ.

Claim 76 (Original): A modified IFNβ cytokine of claim 1, comprising mutations at one or more amino acid residues of IFNβ corresponding to SEQ ID NO:196 at positions corresponding to: 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109,

110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 77: (currently amended): The modified IFNβ cytokine of claim 75, wherein the replacements are selected from the group consisting of amino acid ~~sustitutions~~ substitutions in SEQ ID NO:196 corresponding to: D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position [[136,,]]136, K by H at position 136, E by Q at position

137, E by H at position 137, Y by H at position 163, Y by I at position [[163I,]]163, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 78 (Currently amended): A modified cytokine that is an IFNβ-1 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 197 in the IFNβ-1 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNβ-1.

Claim 79 (Original): A modified cytokine of claim 4 that is an IFNβ-1 cytokine, comprising mutations at one or more amino acid residues of IFNβ-1 corresponding to SEQ ID NO: 197 at positions 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109, 110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 80 (Currently amended): A modified cytokine that is an IFNβ-2a cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 198 in the IFNβ-2a corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNβ-2a.

Claim 81 (Original): A modified cytokine of claim 4 that is an IFNβ-2a cytokine, comprising mutations at one or more amino acid residues of IFNβ-2a

corresponding to SEQ ID NO:198 at positions 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109, 110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 82 (Currently amended): A modified IFN-gamma cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 199 in the IFN-gamma corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFN-gamma.

Claim 83 (Currently amended): A modified cytokine of claim 4 that is an IFN-gamma cytokine, comprising mutations at one or more amino acid residues of IFN-gamma corresponding to SEQ ID NO:199 at positions 33, 37, 40, 41, 42, 58, 61, 64, 65 and 66, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).[[^C]]

Claim 84 (Currently amended): The modified IFN-gamma cytokine of claim 82, wherein the replacements are selected from the group consisting of amino acid ~~sustitutions~~ substitutions in SEQ ID NO:199 corresponding to:

L33V	E41Q	K58Q	D65Q
L33I	E41N	K58N	D65N
K37Q	E41H	K61Q	D66Q,
K37N	E42Q	K61N	
K40Q	E42N	K64Q	
K40N	E42H	K64N	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 84 (Original): The modified IFN-gamma cytokine of claim 82, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO:199 corresponding to:

L33V	E41Q	K58Q	D65Q
L33I	E41N	K58N	D65N
K37Q	E41H	K61Q	D66Q,
K37N	E42Q	K61N	
K40Q	E42N	K64Q	
K40N	E42H	K64N	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 85 (Currently amended): A modified IL-10 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 200 in the IL-10 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-10.

Claim 86 (Original): A modified IL-10 cytokine, comprising mutations at one or more amino acid residues of IL-10 corresponding to SEQ ID NO: 200 at positions 49, 50, 52, 53, 54, 55, 56, 57, 59, 60, 67, 68, 71, 72, 74, 75, 78, 81, 84, 85, 86, and 88, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 87: (Currently amended): The modified IL-10 cytokine of claim 85, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO:200 corresponding to:

K49Q	E50N	L52I	E54Q	E54N
K49N	E50H	L53V		E54H
E50Q	L52V	L53I		D55Q

D55N	L60V	Y72I	E81N
F56I	L60I	E74Q	E81H
F56V	E67Q	E74N	D84Q
K57Q	E67N	E74H	D84N
K57N	E67H	E75Q	P85S
Y59H	M68V	E75N	P85A
Y59I	M68I	E75H	D86Q
	F71I	P78S	D86N
	F71V	P78A	K88Q
	Y72H	E81Q	K88N,

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 88 (Currently amended): A modified erythropoietin cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 201 in the erythropoietin corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified erythropoietin.

Claim 89 (Original): A modified erythropoietin of claim 88, comprising mutations at one or more amino acid residues of erythropoietin corresponding to SEQ ID NO: 201 at positions 43, 45, 48, 49, 52, 53, 55, 72, 75, 76, 123, 129, 130, 131, 162, and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 90 (Currently amended): The modified erythropoietin cytokine of claim 88, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 201 corresponding to:

D43Q	K52Q	E72N	P122S	R131H
D43N	K52N	E72H	P122A	R131Q
K45Q	R53H	L75V	D123Q	R162H
K45N	R53Q	L75I	D123N	R162Q
F48I	E55Q	R76H	P129S	D165Q
F48V	E55N	R76Q	P129A	D165N
Y49H	E55H	P121S	L130V	
Y49I	E72Q	P121A	L130I	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 91 (Currently amended): A modified GM-CSF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 202 in the GM-CSF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified GM-CSF.

Claim 92 (Original): A modified cytokine of claim 91 that is a GM-CSF cytokine, comprising mutations at one or more amino acid residues of GM-CSF corresponding to SEQ ID NO: 202 at positions 38, 41, 45, 46, 48, 49, 51, 60, 63, 67, 92, 93, 119, 120, 123, and 124, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 93 (Currently amended): The modified GM-CSF cytokine of claim 91, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 202 corresponding to:

E38Q	D48Q	K63Q	F119V
E38N	D48N	K63N	D120Q
E38H	L49V	R67H	D120N
E41Q	L49I	R67Q	E123Q
E41N	E51Q	P92S	E123N
E41H	E51N	P92A	E123H
E45Q	E51H	E93Q	P124S
E45N	E60Q	E93N	P124A,
E45H	E60N	E93H	
M46V	E60H	F119I	
M46I			

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 94 (Currently amended): A modified Flt3 ligand cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 203 in the Flt3 ligand corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokine of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified Flt3 ligand.

Claim 95 (Original): A modified Flt3 ligand cytokine of claim 94, comprising mutations at one or more amino acid residues of Flt3 ligand corresponding to SEQ ID NO: 203 at positions 3, 40, 42, 43, 55, 58, 59, 61, 89, 90, 91, 95, and 96, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 96 (Currently amended): The modified Flt3 ligand cytokine of claim 94, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 203 corresponding to:

D3Q	R55Q	P89A
D3N	E58Q	P90S
D40Q	E58N	P90A
D40N	E58H	P91S
E42Q	R59H	P91A
E42N	R59Q	R95H
E42H	K61Q	R95Q
L43V	K61N	F96I
L43I	P89S	F96V,
R55H		

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 97 (Currently amended): A modified IL-2 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 204 in the IL-2 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-2.

Claim 98 (Original): A modified IL-2 cytokine of claim 97, comprising mutations at one or more amino acid residues of IL-2 corresponding to SEQ ID NO: 204 at positions 43, 45, 48, 49, 52, 53, 60, 61, 65, 67, 68, 72, 100, 103, 104, 106, 107, 109, 110, and 132, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 99 (Currently amended): The modified IL-2 cytokine of claim 97, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 204 corresponding to:

K43Q	L53I	E68Q	Y107I
K43N	E60Q	E68N	D109Q
Y45H	E60N	E68H	D109N
Y45I	E60H	L72V	E110Q
K48Q	E61Q	L72I	E110N
K48N	E61N	E100Q	E110H
K49Q	E61H	E100N	L132V
K49N	P65S	E100H	L132I
E52Q	P65A	F103I	E106Q
E52N	E67Q	F103V	E106N
E52H	E67N	M104V	E106H
L53V	E67H	M104I	Y107H,

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 100 (Currently amended): A modified IL-3 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 205 in the IL-3 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-3.

Claim 101 (Currently amended): A modified IL-3 cytokine of claim 100, comprising mutations at one or more amino acid residues of IL-3 corresponding to SEQ ID NO: 205 <u>at positions</u>: 37, 43, 46, 59, 63, 66, 96, 100, 101, and 103, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 102 (Currently amended): The modified IL-3 cytokine of claim 100, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ <u>substitutions</u> in SEQ ID NO:205 corresponding to:

F37I	E59Q	P96A
F37V	E59H	K100Q
E43Q	R63H	K100N
E43N	R63Q	D101Q
E43H	K66Q	D101N
D46Q	K66N	D103Q
D46N	P96S	D103N,

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 103 (Currently amended): A modified SCF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 206 in the SCF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified SCF.

Claim 104 (Currently amended): A modified SCF cytokine of claim 103, comprising mutations at one or more amino acid residues of SCF corresponding to SEQ ID NO: 206 at positions: 27, 31, 34, 37, 54, 58, 61, 62, 63, 96, 98, 99, 100, 102, 103, 106, 107, 108, 109, 134, and 137, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 105 (Currently amended): The modified SCF cytokine of claim 103, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 206 corresponding to:

M27V	D37Q	D54Q	K62Q	F63I	K99Q
M27I	D37N	D54N	K62N	F63V	K99N
K31Q		D58Q		K96Q	
K31N		D58N		K96N	
P34S		D61Q		L98V	
P34A		D61N		L98I	

K100Q	E106H	E134N
K100N	P107S	E134H
F102I	P107A	D137Q
F102V	R108H	D137N,
103Q	R108Q	
K103N	L109V	
E106Q	L109I	
E106N	E134Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 106 (Currently amended): A modified IL-4 cytokine, comprising one or more aminoacid replacements at one or more target positions in SEQ ID NO: 207 in the IL-4 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-4.

Claim 107 (Currently amended): A modified IL-4 cytokine of claim 106, comprising mutations at one or more amino acid residues of IL-4 corresponding to SEQ ID NO: 207 at positions: 26, 37, 53, 60, 61, 64, 66, 100, 102, 103, and 126, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 108 (Currently amended): The modified IL-4 cytokine of claim 106, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 207 corresponding to:

E26Q	E60Q	L66V	E103N
E26N	E60N	L66I	E103H
E26H	E60H	P100S	K126Q
K37Q	K61Q	P100A	K126N,
K37N	K61N	K102Q	
R53H	R64H	K102N	
R53Q	R64Q	E103Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 109 (Currently amended): A modified IL-5 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 208 in the IL-5 cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-5.

Claim 110 (Original): A modified IL-5 cytokine of claim 109, comprising mutations at one or more amino acid residues of IL-5 corresponding to SEQ ID NO: 208 at positions 32, 34, 39, 46, 47, 56, 84, 85, 88, 89, 90, 102, 110, and 111, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 111 (Currently amended): The modified IL-5 cytokine of claim 109, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ <u>substitutions</u> in SEQ ID NO: 208 corresponding to:

R32H	E46N	E47N	K85Q
R32Q	E46H	E47H	K85N
P34S	E47Q	E56Q	E88Q
P34A		E56N	E88N
K39Q		E56H	E88H
K39N		K84Q	E89Q
E46Q		K84N	E89N

E89H	E110Q
R90H	E110N
R90Q	E110H
E102Q	W111S
E102N	W111H,
E102H	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 112 (Currently amended): A modified IL-13 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 209 of an IL-13 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-13.

Claim 113 (Original): A modified IL-13 cytokine of claim 112, comprising mutations at one or more amino acid residues of IL-13 corresponding to SEQ ID NO: 209 at positions 32, 34, 38, 48, 79, 82, 85, 86, 88, 107, 108, 110, and 111, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 114 (Currently amended): The modified IL-13 cytokine of claim 112, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 209 corresponding to:

M32V	E48H	D86N	R110H
M32I	F79I	K88Q	R110Q
W34S	F79V	K88N	F111I
W34H	L82V	R107H	F111V,
L38V	L82I	R107Q	
L38I	R85H	E108Q	
E48Q	R85Q	E108N	
E48N	D86Q	E108H	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 115 (Currently amended): A modified G-CSF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 210 in the G-CSF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified G-CSF.

Claim 116 (Original): A modified G-CSF cytokine of claim 115, comprising mutations at one or more amino acid residues of G-CSF corresponding to SEQ ID NO: 210 at positions 61, 63, 68, 72, 86, 96, 100, 101, 131, 133, 135, 147, 169, 172, and 177, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 117 (Currently amended): The modified G-CSF cytokine of claim 115, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 210 corresponding to:

W61S	F86I	E101N	F147I
W61H	F86V	E101H	F147V
P63S	E96Q	P131S	R169H
P63A	E96N	P131A	R169Q
P68S	E96H	L133V	R172H
P68A	P100S	L133I	R172Q
L72V	P100A	P135S	P177S
L72I	E101Q	P135A	P177A,

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 118 (Currently amended): A modified leptin cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 211 in the leptin corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified leptin.

Claim 119 (Original): A modified leptin cytokine of claim 118, comprising mutations at one or more amino acid residues of leptin corresponding to SEQ ID NO: 211 at positions 43, 49, 99, 100, 104, 105, 107, 108, 141 and 142, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 120 (Currently amended): The modified leptin cytokine of claim 118, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 211 corresponding to:

P43S	P99A	E105Q	D108N
P43A	W100S	E105N	D141Q
L49V	W100H	E105H	D141N
L49I	L104V	L107V	L142V
P99S	L104I	L107I	L142I,
		D108Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 121 (Original): A modified CNTF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 212 in the CNTF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified CNTF.

Claim 122 (Original): A modified CNTF cytokine of claim 121, comprising mutations at one or more amino acid residues of CNTF corresponding to SEQ ID NO: 212 at positions 62, 64, 66, 67, 86, 89, 92, 100, 102, 104, 131, 132, 133, 135, 136, 138, 140, 143, 148, and 151, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 123 (Currently amended): The modified CNTF cytokine of claim 121, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 212 corresponding to:

D62Q	R89Q	E131N	E138H
D62N	E92Q	E131H	D140Q
W64S	E92N	Y132H	D140N
W64H	E92H	Y132I	P143S
E66Q	P100S	K133Q	P143A
E66N	P100A	K133N	D148Q
E66H	E102Q	P135S	D148N
L67V	E102N	P135A	L151V
L67I	E102H	R136H	L151I,
L86V	D104Q	R136Q	
L86I	D104N	E138Q	
R89H	E131Q	E138N	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 124 (Currently amended): A modified LIF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 213 in the LIF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified LIF.

Claim 125 (Original): A modified LIF cytokine of claim 124, comprising mutations at one or more amino acid residues of LIF corresponding to SEQ ID NO: 213 at positions 69, 70, 85, 99, 102, 104, 106, 109, 137, 143, 146, 148, 149, 153, 154, and 156, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 126 (Currently amended): The modified LIF cytokine of claim 124, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 213 corresponding to:

P69S	K102N	D143Q	K153N
P69A	L104V	D143N	D154Q
F70I	L104I	Y146H	D154N
F70V	P106S	Y146I	F156I
R85H	P106A	P148S	F156V,
R85Q	L109V	P148A	
R99H	L109I	D149Q	
R99Q	Y137H	D149N	
K102Q	Y137I	K153Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 127 (Currently amended): A modified oncostatin M cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 214 in the oncostatin M corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified oncostatin M.

Claim 128 (Original): A modified oncostatin M cytokine of claim 127, comprising mutations at one or more amino acid residues of oncostatin M corresponding to SEQ ID NO: 214 at positions 59, 60, 63, 65, 84, 87, 89, 91, 94, 97, 99, 100, 103, and 106, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 129 (Currently amended): The modified oncostatin M cytokine of claim 127, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 214 corresponding to:

E59Q	L65I	R91Q	R100Q
E59N	R84H	K94Q	L103V
E59H	R84Q	K94N	L103I
E60Q	D87Q	D97Q	E106Q
E60N	D87N	D97N	E106N
E60H	E89Q	E99Q	E106H,
R63H	E89N	E99N	
R63Q	E89H	E99H	
L65V	R91H	R100H	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 130 (Currently amended): A modified IL-12 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 215 in the IL-12 corresponding to a structurally-related modified amino acid

position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-12.

Claim 131 (Original): A modified IL-12 cytokine of claim 130, comprising mutations at one or more amino acid residues of IL-12 corresponding to SEQ ID NO: 215 at positions 56, 61, 66, 67, 68, 70, 72, 75, 78, 79, 82, 89, 92, 93, 107, 110, 111, 115, 117, 124, 125, 127, 128, 129, and 189, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 132 (Currently amended): The modified IL-12 cytokine of claim 130, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 215 corresponding to:

K56Q	E72Q	R92H	K117Q
K56N	E72N	R92Q	K117N
E61Q	E72H	K93Q	L124V
E61N	L75V	K93N	L124I
E61H	L75I	E107Q	M125V
L66V	R78H	E107N	M125I
L66I	R78Q	E107H	P127S
E67Q	E79Q	K110Q	P127A
E67N	E79N	K110N	K128Q
E67H	E79H	M111V	K128N
L68V	F82I	M111I	R129H
L68I	F82V	E115Q	R129Q
K70Q	L89V	E115N	R189H
K70N	L89I	E115H	R189Q,

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 133 (Currently amended): A modified hGH cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO:

216 in the hGH corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified hGH.

Claim 134 (Original): A modified hGH cytokine of claim 133, comprising mutations at one or more amino acid residues of hGH corresponding to SEQ ID NO: 216 at positions 56, 59, 64, 65, 66, 88, 92, 94, 101, 129, 130, 133, 134, 140, 143, 145, 146, 147, 183, and 186, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 135 (Currently amended): The modified hGH cytokine of claim 133, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 216 corresponding to:

E56Q	E66Q	L101V	R134Q	D147N
E56N	E66N	L101I	K140Q	R183H
E56H	E66H	E129Q	K140N	R183Q
P59S	E88Q	E129N	Y143H	E186Q
P59A	E88N	E129H	Y143I	E186N
R64H	E88H	D130Q	K145Q	E186H,
R64Q	F92I	D130N	K145N	
E65Q	F92V	P133S	F146I	
E65N	R94H	P133A	F146V	
E65H	R94Q	R134H	D147Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 136 (Currently amended): A modified IL-6 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 217 in the IL-6 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as

assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IL-6.

Claim 137 (Original): A modified IL-6 cytokine of claim 136, comprising mutations at one or more amino acid residues of IL-6 corresponding to SEQ ID NO: 217 at position 64, 65, 66, 68, 69, 75, 77, 92, 98, 103, 105, 108, 133, 138, 139, 140, 149, 156, 178, and 181, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

Claim 138 (Currently amended): The modified IL-6 cytokine of claim 136, wherein the replacements are selected from the group consisting of amino acid ~~stitutions~~ substitutions in SEQ ID NO: 217 corresponding to:

P64S	F73I	R103Q	D139N
P64A	F73V	E105Q	P140S
K65Q	F77I	E105N	P140A
K65N	F77V	E105H	K149Q
M66V	E92Q	E108Q	K149N
M66I	E92N	E108N	W156S
E68Q	E92H	E108H	W156H
E68N	E98Q	D133Q	R178H
E68H	E98N	D133N	R178Q
K69Q	E98H	P138S	R181H
K69N	R103H	P138A	R181Q,
		D139Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 139 (Original): The modified IFNα-2b cytokine of claim 5 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 140 (Original): The modified IFNα-2b cytokine of claim 5 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 141 (Original): The modified IFNα-2b cytokine of claim 5 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 142 (Original): The modified IFNα-2a cytokine of claim 47 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 143 (Original): The modified IFNα-2a cytokine of claim 47 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 144 (Original): The modified IFNα-2a cytokine of claim 47 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in

the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 145 (Original): The modified IFNα-c cytokine of claim 49 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 146 (Original): The modified IFNα-c cytokine of claim 49 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 147 (Original): The modified IFNα-c cytokine of claim 49 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 148 (Original): The modified IFNα-2c cytokine of claim 51 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 149 (Original): The modified IFNα-2c cytokine of claim 51 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 150 (Original): The modified IFNα-2c cytokine of claim 51 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 151 (Original): The modified IFNα-1d cytokine of claim 53 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 152 (Original): The modified IFNα-1d cytokine of claim 53 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 153 (Original): The modified IFNα-1d cytokine of claim 53 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 154 (Original): The modified IFNα-5 cytokine of claim 55 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 155 (Original): The modified IFNα-5 cytokine of claim 55 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 156 (Original): The modified IFNα-5 cytokine of claim 55 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 157 (Original): The modified IFNα-6 cytokine of claim 57 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 158 (Original): The modified IFNα-6 cytokine of claim 57 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 159 (Original): The modified IFNα-6 cytokine of claim 57 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 160 (Claim): The modified IFNα-4 cytokine of claim 59 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 161 (Original): The modified IFNα-4 cytokine of claim 59 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 162 (Original): The modified IFNα-4 cytokine of claim 59 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 163 (Original): The modified IFNα-4b cytokine of claim 61 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 164 (Original): The modified IFNα-4b cytokine of claim 61 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 165 (Original): The modified IFNα-4b cytokine of claim 61 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 166 (Original): The modified IFNα-I cytokine of claim 63 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 167 (Original): The modified IFNα-I cytokine of claim 63 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 168 (Original): The modified IFNα-I cytokine of claim 63 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 169 (Original): The modified IFNα-J cytokine of claim 65 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 170 (Original): The modified IFNα-J cytokine of claim 65 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 171 (Original): The modified IFNα-J cytokine of claim 65 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 172 (Original): The modified IFNα-H cytokine of claim 67 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 173 (Original): The modified IFNα-H cytokine of claim 67 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 174 (Original): The modified IFNα-H cytokine of claim 67 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 175 (Original): The modified IFNα-F cytokine of claim 69 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 176 (Original): The modified IFNα-F cytokine of claim 69 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 177 (Original): The modified IFNα-F cytokine of claim 69 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 178 (Original): The modified IFNα-8 cytokine of claim 71 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 179 (Original): The modified IFNα-8 cytokine of claim 71 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 180 (Original): The modified IFNα-8 cytokine of claim 71 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 181 (Original): The modified IFNα consensus cytokine of claim 73 that has increased stability compared to any of the aligned cytokines, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 182 (Original): The modified IFNα consensus cytokine of claim 73 that has decreased stability compared to any of the aligned cytokines, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 183 (Original): The modified IFNα consensus cytokine of claim 73 that has increased biological activity compared to any of the aligned cytokines, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 184 (Original): The modified IFNβ cytokine of claim 75 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 185 (Original): The modified IFNβ cytokine of claim 75 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 186 (Original): The modified IFNβ cytokine of claim 75 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 187 (Original): The modified IFN β-1 cytokine of claim 78 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 188 (Original): The modified IFN β-1 cytokine of claim 78 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 189 (Original): The modified IFN β-1 cytokine of claim 78 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 190 (Original): The modified IFN β-2a cytokine of claim 80 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 191 (Original): The modified IFN β-2a cytokine of claim 80 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 192 (Original): The modified IFN β-2a cytokine of claim 80 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 193 (Original): The modified IFN-gamma cytokine of claim 82 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 194 (Original): The modified IFN-gamma cytokine of claim 82 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 195 (Original): The modified IFN-gamma cytokine of claim 82 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 196 (Original): The modified IL-10 cytokine of claim 85 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 197 (Original): The modified IL-10 cytokine of claim 85 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 198 (Original): The modified IL-10 cytokine of claim 85 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 199 (Original): The modified erythropoietin cytokine of claim 88 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 200 (Original): The modified erythropoietin cytokine of claim 88 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 201 (Original): The modified erythropoietin cytokine of claim 88 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 202 (Original): The modified GM-CSF cytokine of claim 91 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 203 (Original): The modified GM-CSF cytokine of claim 91 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 204 (Original): The modified GM-CSF cytokine of claim 91 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 205 (Original): The modified Flt3 ligand cytokine of claim 94 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 206 (Original): The modified Flt3 ligand cytokine of claim 94 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 207 (Original): The modified Flt3 ligand cytokine of claim 94 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 208 (Original): The modified IL-2 cytokine of claim 97 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 209 (Original): The modified IL-2 cytokine of claim 97 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 210 (Original): The modified IL-2 cytokine of claim 97 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 211 (Original): The modified IL-3 cytokine of claim 100 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 212 (Original): The modified IL-3 cytokine of claim 100 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 213 (Original): The modified IL-3 cytokine of claim 100 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 214 (Original): The modified SCF cytokine of claim 103 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 215 (Original): The modified SCF cytokine of claim 103 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 216 (Original): The modified SCF cytokine of claim 103 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 217 (Original): The modified IL-4 cytokine of claim 106 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 218 (Original): The modified IL-4 cytokine of claim 106 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 219 (Original): The modified IL-4 cytokine of claim 106 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 220 (Original): The modified IL-5 cytokine of claim 109 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 221 (Original): The modified IL-5 cytokine of claim 109 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 222 (Original): The modified IL-5 cytokine of claim 109 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 223 (Original): The modified IL-13 cytokine of claim 112 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 224 (Original): The modified IL-13 cytokine of claim 112 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 225 (Original): The modified IL-13 cytokine of claim 112 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 226 (Original): The modified G-CSF cytokine of claim 115 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 227 (Original): The modified G-CSF cytokine of claim 115 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 228 (Original): The modified G-CSF cytokine of claim 115 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 229 (Original): The modified leptin cytokine of claim 118 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 230 (Original): The modified leptin cytokine of claim 118 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 231 (Original): The modified leptin cytokine of claim 118 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 232 (Original): The modified CNTF cytokine of claim 121 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 233 (Original): The modified CNTF cytokine of claim 121 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 234 (Original): The modified CNTF cytokine of claim 121 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 235 (Original): The modified LIF cytokine of claim 124 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 236 (Original): The modified LIF cytokine of claim 124 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 237 (Original): The modified LIF cytokine of claim 124 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 238 (Original): The modified oncostatin M cytokine of claim 127 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 239 (Original): The modified oncostatin M cytokine of claim 127 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 240 (Original): The modified oncostatin M cytokine of claim 127 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 241 (Original): The modified IL-12 cytokine of claim 130 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 242 (Original): The modified IL-12 cytokine of claim 130 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 243 (Original): The modified IL-12 cytokine of claim 130 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 244 (Original): The modified hGH of claim 133 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 245 (Original): The modified hGH of claim 133 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 246 (Original): The modified hGH of claim 133 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 247 (Original): The modified IL-6 cytokine of claim 136 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 248 (Original): The modified IL-6 cytokine of claim 136 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 249 (Original): The modified IL-6 cytokine of claim 136 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 250 (Currently amended): A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:

(a) identifying, within a target protein or peptide or plurality thereof, one or more target amino acids, wherein:

each target amino acid is designated an *in silico*-HIT (is-HIT); and

the is-HIT target amino acids are determined by identifying structurally homologous loci between the evolving target protein and a reference protein possessing the desired activity;

(b) identifying one or more replacement amino acids, specific for each is-HIT, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;

(c) producing a population of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein each candidate LEAD protein contains a single amino acid replacement, and wherein each polynucleotide in a set encodes a candidate LEAD protein that differs by one amino acid from the target protein or peptide;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are present in an addressable array; and

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity of an unmodified target protein, wherein each such protein is designated a LEAD mutant protein[[;]].

Claim 251 (Original): The method of claim 250, wherein the predetermined property or activity of the evolved modified protein is increased resistance to proteolysis.

Claim 252 (Original): The method of claim 250, wherein the target proteins comprise a family.

Claim 253 (Original): The method of claim 250, wherein target proteins are cytokines.

Claim 254 (Original): The method of claim 253, wherein the cytokines are selected from the group consisting of interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha (IFNα), interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-

3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

Claim 255 (Original): The method of claim 250, wherein each candidate lead is individually prepared and screened to identify leads.

Claim 256 (Original): The method of claim 250, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids, or the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

Claim 257 (Original): The method of claim 250, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

Claim 258 (Currently amended): The method of claim 250, further comprising:

[[(e)]] (f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

[[(f)]] (g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

[[(g)]] (h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

Claim 259 (Currently amended): The method of claim 258, wherein the nucleic acid molecules in step [[(f)]] (g) are generated by a method selected from among additive directional mutagenesis (ADM), multi-overlapped primer extensions,

oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

Claim 260 (Currently amended): The method of claim 250, wherein candidate [[leads]]LEADs are produced by replacing to a restricted subset of amino acids along the full length of a target protein.

Claim 261 (Original): The method of claim 250, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

Claim 262 (Original): The method of claim 250, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

Claim 263 (Original): The method of claim 258, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

Claim 264 (Currently amended): The method of claim [[250]]258, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

Claim 265 (Original): The method of claim 250, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% compared to the activity of the unmodified target protein.

Claim 266 (Currently amended): The method of claim 250, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% compared to [[he]]the activity of the unmodified target protein.

Claim 267 (Original): The method of claim 250, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater than the activity of the unmodified target protein.

Claim 268 (Currently amended): The method of claim 250, wherein the replacing amino acids are selected using Percent Accepted ~~Mutations~~Mutation (PAM) matrices.

Claim 269 (Original): The method of claim 250, wherein the replacing amino acids are pseudo-wild type amino acids.

Claim 270 (Original): The method of claim 250, wherein identification of the structurally homologous loci between the evolving target protein and a reference protein possessing the desired activity, comprises:

(a) comparing the 3-dimensional structures of the two or more proteins to identify regions of high coincidence between their backbones, said regions designated as structurally homologous regions; and

(b) identifying is-HIT structurally homologous loci on the evolving protein that correspond to structurally related is-HIT amino acid positions within a structurally homologous region of the reference protein.

Claim 271 (Currently amended): The method of claim 270, wherein the comparison of the 3-dimensional structures of the evolving target protein and the reference protein is based upon their ~~3-dimensinal-struoutures~~ 3-dimensional structures, not upon alignment between their respective primary sequences.

Claim 272 (Original): The method of claim 270, wherein the evolving target protein and the reference protein belong to a family of sequence-related proteins.

Claim 273 (Currently amended): The method of claim 270, wherein the evolving target protein and the reference protein ~~belong respectively~~ are non-related proteins or sequence-non-related proteins.

Claim 274 (Original): The method of claim 270, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and the reference protein is in a region selected from the group consisting of:

(a) a small region on the two proteins;

(b) a large region on the two proteins; and

(c) a region that covers the full length of one or both of the proteins.

Claim 275 (Original): The method of claim 270, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and of the reference protein is determined by superposition and RMS deviation calculations using any combination of one or more of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA.

Claim 276 (Original): The method of claim 275, wherein the superposition and RMS deviation calculations are made using all of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA, when present.

Claim 277 (Original): The method of claim 275, wherein the superposition and RMS deviation calculations are carried out on a subset of regions or domains of a larger protein that adopts a structure similar to a smaller protein.

Claim 278 (Currently amended): The method of claim 275, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and the reference protein is obtained using any combination of one or more of either Class Architecture, Topology and Homologous Superfamily (CATH); Combinatorial Extension of the optimal path (CE); Fold Classification based [[of]]on Structure-Structure Alignment of Proteins (FSSP); Structural Classification of Proteins (SCOP); Vector Alignment Search Tool (VAST), and TOP.

Claim 279 (Currently amended): A modified cytokine of claim 1 selected from the group consisting of modified cytokines comprising a sequence of amino acids set forth in any of SEQ ID [[Nos.]]NOS: 2-181, 233-1303 or a structural homolog thereof.

Claim 280 (Original): The modified cytokine of claim 279, selected from the group consisting of interleukin-10 (IL-10), interferon α, interferon β, interferon γ, granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

Claim 281 (Currently amended): A method of generating a modified protein or cytokine having a pre-selected altered phenotype, comprising:

modifying a first protein or cytokine by a directed evolution method to produce an evolved protein or cytokine that has the altered phenotype to identify altered loci; [[and]]

comparing the structures of one or more members of the protein or cytokine family to identify structurally homologous loci for alteration; and

altering the identified loci in members of the protein or cytokine family to produce proteins or cytokines that have the altered phenotype.

Claim 282 (Original): The method of claim 281, wherein directed evolution is effected by a rational directed evolution method.

Claim 283 (Original): The method of claim 281, wherein directed evolution is effected by a 2-dimensional rational scanning.

Claim 284 (Original): The method of claim 281, wherein identification of the structurally homologous loci between the evolved protein or cytokine and members of the protein or cytokine family, further comprises:

(a) comparing the 3-dimensional structures of the evolved protein or cytokine with one or more members of the protein or cytokine family to identify regions of high coincidence between their backbones, said regions designated as structurally homologous regions; and

(b) identifying is-HIT structurally homologous loci on the members of the protein or cytokine family that correspond to structurally related is-HIT amino acid positions within a structurally homologous region of the evolved protein or cytokine.

Claim 285 (Original): The method of claim 284, wherein the comparison of the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is made irrespective of any alignment between their respective sequences.

Claim 286 (Original): The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is in a region selected from the group consisting of:

(a) a small region on the two proteins;

(b) a large region on the two proteins; and

(c) a region that covers the full length of one or both of the proteins.

Original 287 (Original): The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and of the evolved protein or cytokine is determined by superposition and RMS deviation calculations using any combination of one or more of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA.

Claim 288 (Currently amended): The method of claim 287, wherein the superposition and RMS deviation calculations are made using all of the peptide backbone atoms present selected from <u>the</u> group [[the]] consisting of: N, C, C(C=O), O and CA.

Claim 289 (Original): The method of claim 287, wherein the superposition and RMS deviation calculations are carried out on a subset of regions or domains of a larger protein that adopts a structure similar to a smaller protein.

Claim 290 (Currently amended): The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is obtained using any combination of one or more of either CATH (Class Architecture, Topology and Homologous Superfamily); CE (Combinatorial Extension of the optimal path); FSSP (Fold Classification based [[of]]<u>on</u> Structure-Structure Alignment of

Proteins); SCOP (Structural Classification of Proteins); VAST (Vector Alignment Search Tool), and TOP.

Claim 291 (Currently amended): The method of claim 283, wherein the 2-dimensional rational scanning method comprises:

(a) identifying, within the first protein or cytokine, one or more target amino acids amenable to providing the altered phenotype upon amino acid replacement, wherein each target amino acid is designated an *in silico*-HIT (is-HIT);

(b) identifying one or more replacement amino acids, specific for each is-HIT, amenable to providing the altered phenotype upon amino acid replacement, wherein each single amino acid replacement within the protein or cytokine is designated as a candidate LEAD protein;

(c) producing a population of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein each candidate LEAD protein comprises a single amino acid replacement, and wherein each polynucleotide in a set encodes a candidate LEAD protein that differs by one amino acid from the unmodified protein or cytokine;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are present in an addressable array; and

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more candidate LEAD proteins that has activity that differs from the unmodified protein or cytokine, wherein each such protein is designated a LEAD mutant protein.

Claim 292 (Original): The method of claim 291, wherein the array comprises a solid support with wells; and each well contains one set of cells.

Claim 293 (Original): The method of claim 291, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids.

Claim 294 (Original): The method of claim 291, wherein the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

Claim 295 (Original): The method of claim 291, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

Claim 296 (Original): The method of claim 291, further comprising:

(f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified protein or cytokine and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

Claim 297 (Original): The method of claim 296, wherein the nucleic acid molecules in step (f) are produced by a method selected from among Additive Directional Mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

Claim 298 (Original): The method of claim 291, wherein the is-HITs identified in step (a) correspond to a restricted subset of amino acids along the full length target protein.

Claim 299 (Original): The method of claim 291, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

Claim 300 (Original): The method of claim 291, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

Claim 301 (Original): The method of claim 296, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

Claim 302 (Currently amended): The method of claim [[291]]296, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified protein or cytokine.

Claim 303 (Original): The method of claim 291, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the activity of the unmodified target protein.

Claim 304 (Currently amended): The method of claim 291, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or [[100%,]]100% of the activity of the unmodified target protein.

Claim 305 (Original): The method of claim 291, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater or less than the activity of the unmodified target protein.

Claim 306 (Original): A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, [[IFN-2c]]IFNα-2c cytokine selected from the group consisting of proteins comprising one or more single amino acid replacements corresponding to the replacement of: N by D at position 45; D by G at position 94; G by R at position 102; A by G at position 139; or any combination thereof.

Claim 307 (Currently amended): A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, [[IFN-2c]]IFNα-2c cytokine ~~selected from~~ selected from the group consisting of proteins comprising one or more single amino acid replacements in any of SEQ ID [[Nos.]]NOS: 1, 182, 185 or 232 or any combination thereof corresponding to the replacement: L by V at position 3; L by I at position 3; P by S at position 4; P by [[by]] S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L

by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165 or any combination thereof, wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

Claim 308 (Currently amended): A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, [[IFN-2c]]IFNα-2c cytokine selected from ~~selected from~~ the group consisting of proteins comprising one or more single amino acid replacements in any of SEQ ID [[Nos.]]NOS: 1, 182, 185 or 232 or any combination thereof corresponding to the replacement L by V at position 3; L by I at position 3; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83;

K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; E by H at position 165; N by D at position 45; D by G at position 94; G by R at position 102; and A by G at position 139, wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID [[No.]]NOS: 1 or 182.

Claim 309 (Original): The modified cytokine of claim 1, that is an interferon β (IFNβ).

Claim 310 (Currently amended): A modified IFN β cytokine of claim 309 selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID [[NOS:]]NO:196, corresponding to the replacement of M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L

by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R

by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T

at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at

position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90,

wherein residue 1 corresponds to residue 1 of the mature IFNβ cytokine set forth in SEQ ID NO:196.

Claim 311 (Original): A modified cytokine of claim 1 that comprises one or more pseudo-wild type mutations.

Claim 312 (Original): The modified cytokine of claim 311 that is a modified IFNβ.

Claim 313 (Original): A modified IFNβ cytokine of claim 309 that has increased antiviral activity compared to the unmodified cytokine.

Claim 314 (Currently amended): The modified IFNβ cytokine of claim 313, wherein antiviral activity is assessed by measuring replication by reverse transcription quantification PCR (RT-qPCR) or CPE ~~(cythopathic effect)~~ (cytopathic effect).

Claim 315 (Currently amended): A modified IFNα-2b or IFNα-2a cytokine of claim [[309]] 308 that has more antiviral activity than antiproliferative activity compared to the unmodified cytokine.

Claim 316 (Original): The cytokine of claim 315, wherein antiproliferative activity is assessed by measuring cell proliferation in the presence of the cytokine.

Claim 317 (Original): A modified IFNβ cytokine of claim 309 that binds to an IFN receptor, but exhibits when compared to unmodified IFNβ, decreased antiviral activity and decreased antiproliferative activity relative to its receptor binding activity.

Claim 318 (Original): A modified cytokine of claim 1, comprising two or more mutations.

Claim 319 (Original): A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

Claim 320 (Original): A modified cytokine that exhibits greater resistance to proteolysis compared to the unmodified cytokine, comprising one or more amino acid replacements at one or more target positions on the cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNβ modified cytokines of claim 309.

Claim 321 (Currently amended): A modified cytokine of claim 320, wherein the resistance to proteolysis is measured by mixing it with a protease ~~in vitro,~~ *in vitro*, incubation with blood or incubation with serum.

Claim 322 (Original): A cytokine structural homolog of an IFNβ modified cytokine of claim 309, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of the modified IFNβ.

Claim 323 (Original): A cytokine homolog of claim 322, wherein the homolog has increased resistance to proteolysis compared to its unmodified cytokine counterpart, wherein the resistance to proteolysis is measured by mixture with a protease *in vitro*, incubation with blood, or incubation with serum.

Claim 324 (Currently amended): A modified IFNβ cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID [[NO.]]NO: 196 in the IFNβ corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNβ modified cytokines of claim 309, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or [[a]] with a blood lysate or by incubation with serum, compared to the unmodified IFNβ.

Claim 325 (Original): The modified IFNβ cytokine of claim 309 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 326 (Original): The modified IFNβ cytokine of claim 309 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the

appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 327 (Original): The modified IFNβ cytokine of claim 309 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

Claim 328 (Currently amended): A modified of IFNβ cytokine of claim 309, selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID [[NOS:]]NO:196, or any combination thereof, corresponding to the replacement of: M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at

position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y

by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by

D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90,

wherein residue 1 corresponds to residue 1 of the mature IFNβ cytokine set forth in SEQ ID [[NOS:]]NO:196.

CLaim 329 (Currently amended): A modified IFNβ cytokine of claim 309 selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID [[NOS:]]NO:196, or any combination thereof, corresponding to the replacement of: D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position

163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 330 (Currently amended): A modified IFNβ cytokine of claim 309 selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID [[NOS:]]NO:196, or any combination thereof, corresponding to the replacement of: M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at

position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by

E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86,

N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at

position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

Claim 331 (Currently amended): A modified IFNβ of claim 330 selected from the group consisting of a modified IFNβ set forth in any of SEQ ID [[Nos.]]NOS:234-289, 989-1302.

REMARKS

Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

Claims 1-331 are pending in this application. Claims 1, 2, 5, 6, 13-15, 20, 23, 31, 33, 35, 39, 41-43, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 69, 71, 73, 75, 77, 78, 80, 82-85, 87, 88, 90, 91, 93, 94, 96, 97, 99-108, 111, 112, 114, 115, 117, 118, 120, 121, 123, 124, 126, 127, 129, 130, 132, 133, 135, 136, 138, 250, 258-260, 264, 266, 268, 271, 273, 278, 279, 281, 288, 290, 291, 302, 304, 306-309, 314, 315, 321, 324, and 328-331 are currently amended. The amendment to claim 31 replaces the word "cell" with "host". This amendment finds basis in claim 31, line 3 in which it is stated "...introducing a nucleic acid of claim 26 into a host...". Claim 33 is amended to clarify claim dependency. Claim 35 is amended to clarify claim dependency. Claim 35 currently depends upon claim 34, which depends upon claim 31 and further describes the host as a eukaryotic host cell. Claim 35 further describes the cytokine of claim 31. Hence, for the sake of clarity, claim 35 is amended to refer to the "...method of claim 31...". Claim 75 is amended to replace "IFNα-β" with "IFNβ". This amendment finds basis in the claim which points to SEQ ID NO: 196 as the cytokine. SEQ ID NO: 196 is the sequence for Interferon beta. Claim 258 is amended to correct the lettering of the elements further to claim 250, on which claim 258 depends. Claim 259 is amended to correct the lettering of the elements further to claim 258, on which claim 259 depends. Claim 260 is amended to change the case of the word "leads" to "LEADs". This amendment finds basis on page 18, line 25 of the specification where "LEADs" and "Candidate LEADs" are defined. Claim 264 is amended to correct claim dependency. Claim 250, which describes "candidate LEADs" does not have the proper antecedent basis for claim 264, which further describes "LEADs" and "super-LEADs". However, claim 258 describes "super-LEADs" and does have the proper antecedent basis for claim 264. Claim 302 is amended to correct claim dependency. Claim 291, which describes "candidate

LEADs" does not have the proper antecedent basis for claim 302, which further describes "LEADs" and "super-LEADs". However, claim 296 describes "super-LEADs" and does have the proper antecedent basis for claim 302. Claims 306, 307 and 308 are amended to replace "IFN-2c" with "IFNα-2c". This amendment finds basis in the specification on page 86, line 4. Claim 315 is amended to correct claim dependency. Claim 315 further describes modified interferon alpha cytokines, but currently depends upon claim 309, which describes an interferon beta cytokine. Thus, claim 315 should depend upon claim 308, which describes interferon alpha cytokines.

All other claims are amended to correct minor typographical and spelling errors.

The amendments to the specification are to correct obvious typographical and spelling errors. The amendment on page 1, line 18, replaces the phrase which reads "...Attorney docket no. 37851-923..." with "...U.S. application Serial No. 10/658,355...". The amendment finds basis in the cited application which was filed on the same day as the present application and therefore no serial number was available at the time the present application was drafted and filed.

The amendment on page 41, line 17, replaces the phrase which reads "...Attorney docket no. 923..." with "...10/658,355...". The amendment finds basis in the referenced application which was filed on the same day as the present application and therefore no serial number was available at the time the present application was drafted and filed.

The amendment on page 75, line 1, replaces the phrase which reads "...decrease the viral activity..." with "...decrease the antiviral activity...". This amendment finds basis on page 3, lines 4-6 in which the "antiviral" effects of the Interferon alphas are defined.

The amendment on page 81, lines 27-28, replaces the phrase which reads "...http://scop.mrc-lmb.cam.ac.uk/scop/..." with "...scop.mrc-lmb.cam.ac.uk/scop/..." to remove the executable from the specification.

The amendment on page 95, line 19, adds to the phrase "...(see, copending)..." the inadvertently omitted phrase which reads "...U.S. application Serial No. 10/658,355, filed the same day herewith, based on U.S. provisional application Serial Nos. 60/457,063 and 60/410,258)...". This amendment finds basis in the specification on page 41, lines 15-21 in which the copending application is identified.

The amendment on page 131, line 31, replaces the phrase which reads "...43 Mm..." with "...43 mM..." to reflect the appropriate abbreviation for millimolar concentration.

No new matter has been added to the specification.

* * *

Entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,

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